BOTULINUM TOXIN TYPE-A TO TREAT DROOLING

A STUDY IN CHILDREN WITH CEREBRAL PALSY

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CIP-DATA KONINKLIJKE BIBLIOTHEEK, DEN HAAG

Jongerius, Peter H.

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Thesis, Nijmegen. With ref.- With summary in Dutch

ISBN: 90-9018510-0

Subject heading: drooling & sialorrhea / Botulinum Toxin / Botox® / saliva / salivary gland(s) / cerebral palsy / child / ultra sound / anticholinergic drug / systematic review / Quality of Life

Cover drawing: P Tacoma
Cover Design: Ans Wilders
Lay out: Scriptura, Nijmegen
Printed by: Quick Print BV, Nijmegen

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A STUDY IN CHILDREN WITH CEREBRAL PALSY

BOTULINE TOXINE TYPE-A VOOR DE BEHANDELING VAN ERNSTIG SPEEKSELVERLIES

EEN STUDIE BIJ KINDEREN MET EEN CEREBRALE PARESE

Een wetenschappelijke proeve op het gebied van de
Medische Wetenschappen

Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de Rector Magnificus
Prof. Dr. C.W.P.M. Blom,
volgens besluit van het college van Decanen
in het openbaar te verdedigen op
woensdag 10 November 2004
des namiddags om 3.30 uur precies

door

Pieter Hendrik Jongerius

geboren op 17 November 1955
te Oosterbeek

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This PhD study was conducted in collaboration with the departments of pediatric neurology (Prof J. J. Rotteveel MD PhD), rehabilitation medicine (Prof F.J.M. Gabreëls MD PhD), and otorhinolaryngology (Prof K. Graamans MD PhD) at the Radboud University Nijmegen, Medical Centre, the Netherlands, together with the department of epidemiology/methodology (J. van Limbeek MD PhD) of the "St.Maartenskliniek", specialized hospital for rehabilitation, orthopaedics and rheumatology, Nijmegen, the Netherlands.

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The medication (Botox®) was provided by Allergan BV, Nieuwegein, the Netherlands.
This research program and the publications were financially supported by The Johanna Kinder Fonds, Arnhem.
Additional grands were received from Allergan BV, Nieuwegein; Medtronic BV, Heerlen; POM, Nijmegen; Levit orthopaedic BV, Amsterdam.
The author and his supervisors gratefully thank the departments of rehabilitation medicine, pediatric neurology, otorhinolaryngology, radiology, and anesthesiology of the Radboud University Nijmegen, Medical Centre, as well as the department of rehabilitation of the "St. Maartenskliniek" for their unrestricted support.

Opgedragen aan Lina, Femke en Roeland
Voor mijn Moeder
Denkend aan mijn Vader

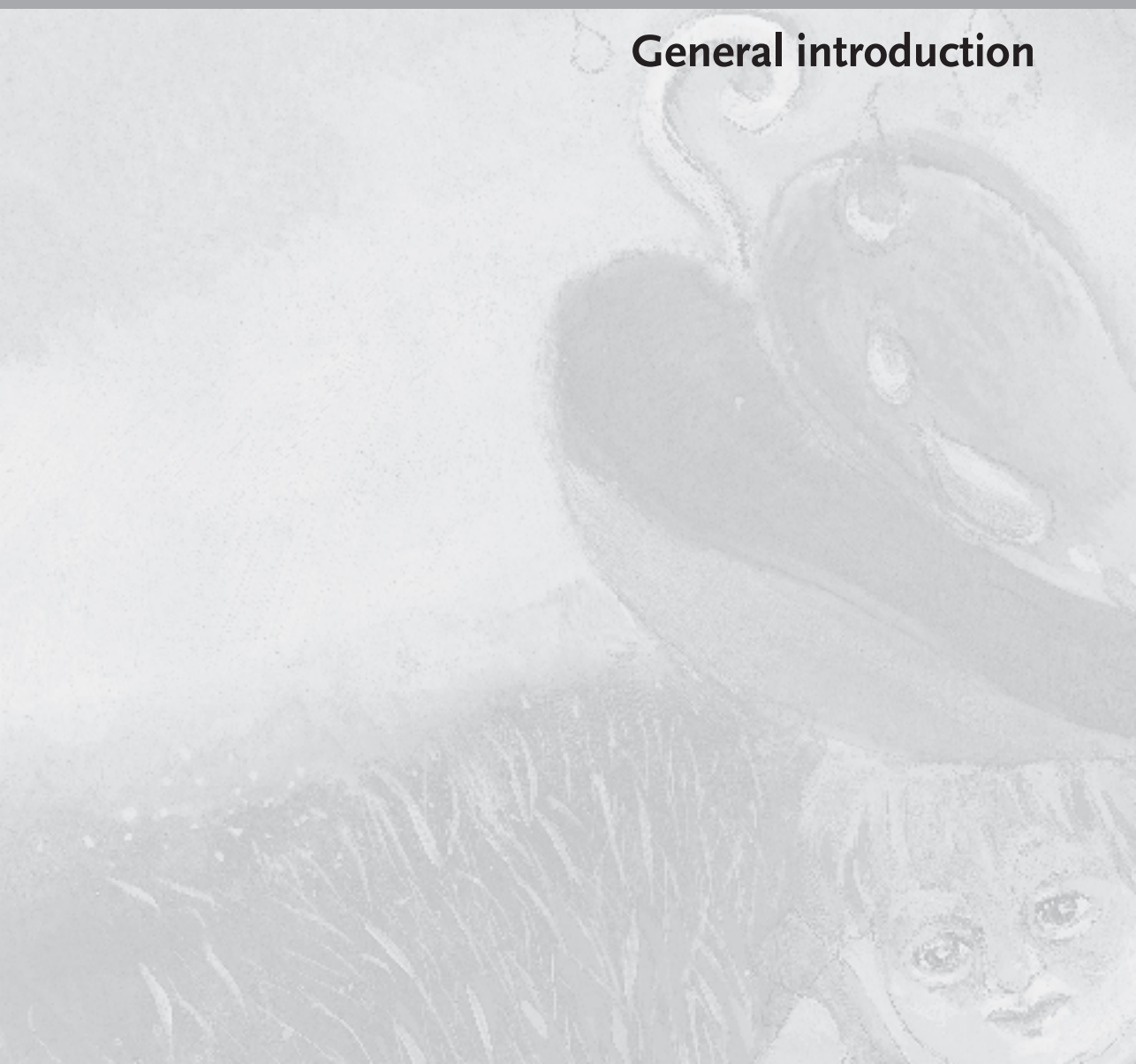
Contents

List of abbreviations

ANOVA	Analysis of variance
BoNT	Botulinum Neuro Toxin type-A
BW	Body weight
CLOF	Carrying the last observation forward
cm	Centimeter
CNS	Central nervous system
CP	Cerebral palsy
df	Degrees of freedom
DQ	Drooling Quotient
H	Hour
i.m.	Intramuscular
IE	Infantile encephalopathy
IQ	Intelligence quotient
ITT	Intention to treat
kDa	Kilo Dalton
LD50	50% Lethal Dose
Locf	Last observation carried forward
MANOVA	Mulpiple analysis of variance
min	Minute
ml	Milliliter
mm	Millimeter
mo	Month(s)
MV	Missing value
N	Number of subjects
NA	Not Applicable
ND	Not Described
ng	Nano gram
NS	Not significant
p	Probability
p.o.	by mouth
ParFL	Parotid salivary flow
pH	Negative logarithm of hydrogen ion activity
QoL	Quality of life
r	correlation coefficient
RCT	Randomized clinical trial
SD	Standard deviation
SL	Sublingual gland
SM	Submandibular gland
SNAP	Synaptosomal associated protein
SNARE	Soluble N-ethyl-maleimide sensitive factor attachment protein receptor
SPSS	Statistical Products and Service Solutions
SS	Scaled scores
SubFL	Submandibular salivary flow
SW	Within-subjects standard deviation
TDS	Teacher drooling scale
TotFl	Total salivary flow
TS	Total scores
UMNS	Upper motor neuron syndrome
V	Validity
VAS	Visual analog scale
WCS	Worst case scenario
wk	Week(s)
Yr	Year(s)

Chapter 1

General introduction



1.1 Drooling

1.1.1. General remarks

Physicians working in pediatric care are confronted with a number of impairments, disabilities, and related problems in social participation. The specialist for rehabilitation medicine has the explicit task to propose, execute and coordinate adequate therapy programs during developmental ages of the handicapped child. In the enormous range of possible treatment options it can be difficult to decide about priorities and to choose the optimal treatment with respect to the childs phase of life and its perpectives. In collaboration with the parents and other team members the doctor should carefully weigh the pros and cons of any intervention with respect to the benefit and the disadvantages for the child: physically as well as emotionally. With regard to time-management in medical practice it can almost be regarded as an art to secure that existing impairments and problems get enough attention. The motivation must always be to optimize the child's opportunities to develop, depending on his or her functional status.

By far, impairments and disabilities of movement and posture get the greatest attention of workers in the field of rehabilitation. The efforts to gain improvement in stature and gait are encouraged by parents desperately trying to stimulate independent mobility for their child, which is generally considerate to be one of the most important goals to achieve. Apart from mobility, oral-motor achievements are of great importance for social functioning with speech definitely as the most appreciated capability. Oral motor skills, resulting in adequate handling of saliva and food, are important conditions for oral integrity that support social acceptance and integration. Impairment in basic functions such as sucking, swallowing, breathing, and coughing will frequently result in clinical problems of which drooling is an example. Drooling is clinically expressively apparent in one of three cases of children with cerebral palsy (CP). It is one of the problems that may be ignored or over-looked in the wide variety of disabilities the child is confronted with.

Drooling in children with CP is the central theme in this thesis: a complex problem that is difficult to treat. In fact, it is a problem that the child and his parents have to cope with. Blasco's definition is often quoted: "drooling is the unintentional loss of saliva and contents from the mouth". It is a normal clinical manifestation in the growing child, up to the age of 18 months[1]. Crysdale argued that drooling beyond the age of four

[1] *www.droolinginfo.org*

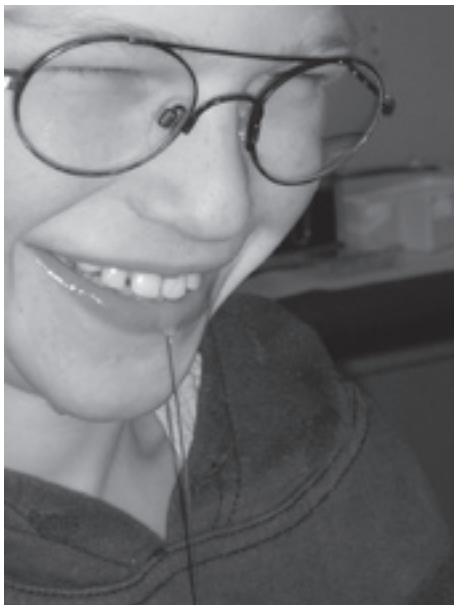
is considered as abnormal[2]. Nevertheless, drooling frequently persists in children with poor neuromuscular coordination, mental retardation or learning disabilities, as well as in patients who have lost the structural integrity of their jaws, lips or oral cavity[3-5]. The dribbled saliva will soil furniture, carpets, toys, books and clothing. Even the clothing of caretakers may become wet. In modern times there is risk that computers, communication aids and other electronic devices are damaged.

1.1.2. Drooling in cerebral palsy

The prevalence of drooling has been studied in only a small number of studies. A considerable diversion in outcome exists. The results of these studies cannot be straightforwardly compared due to a variation in research design, patient selection, and data presentation. The main problem seems to be the quantification of salivary flow rate or drooling for research purposes. Salivary flow can vary from minute to minute depending on factors such as hunger, thirst, fatigue, anxiety, and excitement. Other influences are the circadian rhythm and changes over time. In previous studies drooling has been reported to be a significant problem in about 10% of a Swedish population of children with cerebral palsy showing 'embarrassing drooling'[6]. In another study children with CP showed moderate to serious drooling in about 10 to 37.4% of cases[7]. In a recent study the prevalence of drooling was investigated in a population across dental age. Sixty-eight percent of the patients suffered from spasticity of which 45% had a quadriplegia. Of the total population, 58% had a drooling condition to some extent (33% severe drooling, 9% moderate drooling and 16% mild drooling). The authors concluded that the degree of drooling decreased as the dental age increased[8].
Although no definite conclusion can be drawn from the literature it seems reasonable to accept that one out of three children with cerebral palsy drools to some extend (Fig 1.1). Saliva spilled from the mouth is referred to as anterior drooling, which is clearly visible. This must be separated from posterior drooling in which saliva, probably mixed with food components, is spilled through the faucial isthmus creating a great risk of aspiration.

Drooling influences the individuals' health in some respects[1;9-12]. Children suffering from severe drooling frequently have a chronically irritated, chapped, or macerated skin over the chin and peri-oral region leading to cheilitis in 67% of cases[13]. In cool weather the dampness from saliva is chilling and spilled saliva may even freeze if too little attention is paid. Although seldom of clinical relevance, there may be chronic loss

Figure 1.1: The child with cerebral palsy and severe drooling



Printed with approval of the parents.

of fluid and nutrients. Serous problems with respect to general health are related to posterior drooling. Children with inadequate swallowing activities frequently aspirate their own saliva, which in turn may cause recurrent pneumonia.

Some authors recognize drooling as one of the most common dysfunctions in children with CP and perhaps the most problematic in terms of social environment and relationship [12;14;15]. The diversity of the problem has been documented during a consensus meeting in 1991 organized by P.A. Blasco and the consortium on drooling[16]. The constant presence of saliva will impair articulation and the possibilities of effective and satisfactory communication. The unsightly nature and odor, in combination with salivary spray when the individual talks, sneezes or coughs can result in a degree of social alienation from peers and other members of society. The involved children will receive fewer hugs and kisses since drooling is cosmetically unappealing[1;11;12]. Drooling is stigmatizing and the individual may not succeed to fully integrate into society[11;17]. It must be emphasized that drooling children are frequently underestimated with respect to their mental capacities.

Generally, drooling tends to be worse if there is moderate or severe mental retardation. Patients of normal intelligence who are aware of the problem are less likely to interact with other children concerning normal peer activities[10;18-21]. "The distress and social

stigma of continuous drooling is so disturbing to even the moderately retarded child that many consider it their worst affliction"[18].

Drooling is not only a problem for the child itself but is also of serious social and emotional meaning to the family. Bachrach et al asked parents of more than 1400 patients with CP to complete questionnaires that included a question about drooling[22]. Thirty-four percent indicated that drooling was sometimes a problem 'requiring a bib', and 16% responded that it was often a problem 'requiring daily clothing changes'. Caretakers such as parents, teachers, and therapists often spend much time in suctioning and cleaning the child's mouth or changing cloths. Drooling warrants treatment when it interferes with the patient's well-being[23].

1.1.3. The mechanism of drooling

The submandibular glands are the main paired glands producing about 70% of high viscosity resting saliva[14]. In addition, resting saliva is composed of secretions from the parotid glands (~ 25%) and the sublingual glands (~ 5%). The large parotid glands are capable of producing great amounts of watery saliva that is secreted promptly as a reaction to tactile or gustatory stimulation of the oral mucosa for example during eating or drinking. Authors generally agree that the saliva production is within normal limits in CP. Hypersalivation or hypersialorrhea, a situation in which excessive secretion of saliva occurs, is rarely recognized in drooling children with cerebral palsy[7;15;24-27].

The normal pathway of saliva from the oral cavity to the esophagus depends on cognitive awareness of social norms, an intact sensitivity in the oral region, and a well developed coordination of oro-facial, palato-lingual and head- and neck musculature. Due to developmental retardation and oral movement disorders, primary functions such as sucking, chewing and swallowing may be disturbed starting predominantly at early age. One out of 3 children suffering from CP is considerate to have serious oral impairment. About 90% of cases are recognized in preschool and school age[28]. Mal-coordination of muscles involved in the oral stage of swallowing leads to excessive pooling of saliva in the anterior mouth with resultant loss of saliva from the mouth[12]. Disorders of tongue mobility are the most common finding encountered in drooling children. Constant tongue thrusting may lead to proclination of the upper teeth, further deteriorating the anatomy. Tongue trusting activities are normally present at birth to aid sucking but should disappear at around the age of three months.

The absence of lip closure is probably a causative as well as an aggravating factor. Effective lip closure is sometimes prevented by spastic contractions of the mouth-floor

muscles or the upper-lip elevator muscle. The effect of insufficient mouth closure on drooling has been reported[4]. Harris described drooling children with CP swallowing inefficient also demonstrating a poor synchrony of lip closure[3]. Lip closure is an important condition to build up negative pressure during the oral phase of swallowing. In a study with a group of unaffected children, a group of drooling CP children and a group of non-drooling children with CP the oral phase of swallowing was investigated[29]. This phase is characterized by two stages. During the 'suction' stage liquid placed under the tongue or behind the lower lip, is sucked over the tongue and then propelled towards the pharynx. In contrast to normal children and non-drooling children with CP it was demonstrated that 57.5% of the drooling children with CP did not close their lips during swallowing. Residual liquid in the mouth after swallowing occurred in 78.1% of the drooling children. The second 'propelling' stage did not differ between the drooling children and the other two groups. Koheil et al found that the pharyngeal and esophageal phases of swallowing in normal subjects and drooling patients were similar[30]. In addition, Sochaniwskyj suggested children with CP to differ from normal children in their lower frequency of conscious swallowing[31].

Other contributing conditions to drooling are a decreased intra-oral sensitivity and a hypo-active gag reflex. The relation between oral sensation and drooling was investigated by Weiss-Lambrou et al. Children with drooling scored significantly lower on tests of oral sensation than did non-drooling patients[32].

Children with CP frequently have stasis of saliva in their mouth located sublingually and in the buccal pools. Due to incoordinate movements saliva may find its' way to the posterior side of the tongue and leak into the hypopharynx. This 'posterior drooling' may be apparent because it often presents with congested breathing or a loud and alarming rattle in the throat. Because of unrecognized aspiration recurrent silent pneumonia may occur. This morbidity leads to anxiety and refusal to swallow[33;34]. The risk of posterior drooling can be enhanced by the fact that many of the patients are taken care of in a supine position during a substantial part of the day.

A complex interaction exists between gastro esophageal reflux and salivary flow rate. In healthy subjects, exposure of the distal esophagus to the acid contents of the stomach results in an immediate increase of saliva secretion. The assumed function of this is that swallowed saliva plays a role in the defense against acid-induced injury to the esophageal mucosa. It is suggested that reflux in children with CP causes stimulation of pH-sensitive receptors in the distal esophageal mucosa, which activates the esophageal-salivary reflex leading to an increase of salivary flow rate[35;36].

Chronic gastro esophageal reflux itself is a well-known clinical entity causing aspiration with recurrent pneumonia[37-39]. Up to 60% of severely impaired children may aspirate[40]. Aspiration aggravates when the situation is complicated by inefficient posture or deformity of the spine and trunk.
Because of the esophageal-salivary reflex, gastro esophageal reflux may cause deterioration of either anterior or posterior drooling.

1.1.4. The treatment of drooling

The goal of any drooling treatment will be a reduction in visible spill of saliva or a decrease of posterior drooling. Non-invasive therapies to reduce drooling comprise: 1) behavioral techniques, 2) speech therapy (early intervention by oral neurodevelopmental techniques) to optimizing oral sensation and to train oral motor skills, 3) the administration of anticholinergic drugs, and 4) (intra-ductal) radiation. Surgical procedures include: 1) salivary gland excision, 2) salivary duct rerouting, or 3)a combination of these. Other less successful techniques have been performed like Chorda tympani neurectomy to eliminate parasympathetic stimulation to the salivary gland.
The intra-glandular injection of Botulinum toxin is a non-surgical approach, although invasive with the need of injections and of anesthesia, in children.
The above-mentioned interventions differ in their basic approach. The first option for treatment is to modify and optimize the individuals' capability to handle the secreted saliva. Behavioral therapy, oral-motor therapies, or specific handling techniques by the speech therapist are generally used.
A second strategy encompasses procedures designed to reduce salivary flow in order to diminish drooling. This can be achieved by reduction of secretion from the parenchyma e.g. radiation of the salivary gland, neurectomy, anticholinergic drugs, intra-glandular Botulinum toxin injections, or by blocking the salivary flow after its secretion e.g. legation of the salivary ducts. A more rigorous way is to excise salivary glands.
The final category of interventions comprises procedures intending to re-direct the salivary flow in order to support oral management of saliva e.g. rerouting of a salivary ducts.
The mode of drooling treatment will depend on a variety of factors such as age, medical diagnosis, the general state of health, mental ability, the anatomy of the oro-facial region, and the severity and frequency of drooling. Diverting opinions exist as to what

would be the best management. Some authors abominate surgical procedures pointing at the operation risks, also fearing for possible adverse effects and the irreversibility of the interventions. In general, surgery is recommended only if conservative measures fail to reduce drooling. Among many surgeons the question is whether such an attitude is still defensible given the overall good results of surgery presented in the literature[41]. Surgical interventions are advocated as a definite solution for drooling; the re-routing of Wharton's ducts in combination with excision of the sublingual glands being the present standard procedure[2;42]. In a letter to the editor Blasco reacted to this, writing: "The general conclusion that 'each of the surgical procedures described has its devotees and detractors' is an understatement, and this apparent bias renders the surgical literature on this subject uncommonly difficult to interpret. At a conference in 1999, known as the Blasco Statement, concern was voiced that the severity of surgical complications is generally underreported and under-emphasized" [1;16].

A review of the surgical literature shows serious side effect such as wound dehiscence, parotitis, cysts, stenosis, and fistulae. Nearly all of the patients will have transient postoperative facial or cheek swelling for a few days. Parents have to be informed that tube feeding might be required during this period. Hospital stay ranges from 3 to 7 days among the different authors[18;43].

In the discussion about conservative measures it is stated that success rates are low and demand great efforts of caregivers and substantial time investment of the health-care system, with related costs. Solicitors of the non-surgical approach plea for a thorough evaluation and instruction by the speech therapist focused on oral stimulation or eating and drinking programs.

Occupational-, physical-, and speech therapists have used handling techniques and assistance equipment to help control drooling. Primary goals are: enhancing head control, normalizing muscle tone, stabilizing body posture, promoting jaw stability, eliciting mouth and lip closure, decreasing tongue-thrust, and facilitating swallowing.

The application of anticholinergic drug is more or less regarded as the classical way to treat drooling. To date the long term use of anticholinergics is no longer advised because of serious side effects occurring in most patients[44].

In 1999 a conference of the drooling consortium took place to elaborate consensus about the strategy of the treatment of socially disabling drooling[16]. Based on this declaration and given the recently added possibility of Botulinum toxin treatment, the interventions to manage saliva or to treat drooling can be categorized into conservative measures, non-surgical/invasive interventions, and surgical procedures (Table 1.1)

Table 1.1: Schematic presentation of the treatment options for drooling

	Conservative measures	**Non-surgical/ invasive interventions**	**Surgical procedures**
Approach/interventions	speech therapy, occupational and physical therapy	intra-glandular BoNT* injections	rerouting of Whartons' ducts in combination with sublingual gland excision
Effect	Improvement of oral motor skills and regulation of sensibility Reduction of tongue trusting Improvement of swallowing Improvement of body posture	Re-direction of salivary flow rate	Re-direction of the salivary flow
Duration of effect	As long as therapy is continued	6 to 12 months Probably longer intervals if repeated injections are given	Definite
Adverse effects	None	None Only if BoNT is wrongly injected as can happen when no ultrasound guidance is used	Varying, dependent on the specific approach Infection, nerve damage, Ranulae, swelling with consequent feeding problems, Stenosis, fistulae.
Contra-indications	None	Previous surgical intervention in one of the major salivary glands. Known hypersensibility to Botulinum toxin or any other part of the formulation	Disturbed pharyngeal or esophageal phase of swallowing. A history with recurrent aspiration. Prior surgery of the parotids
Preferred age groups	Not specified	4 years and older	7 years and older

*BoNT: Botulinum Neuro Toxin Type-A

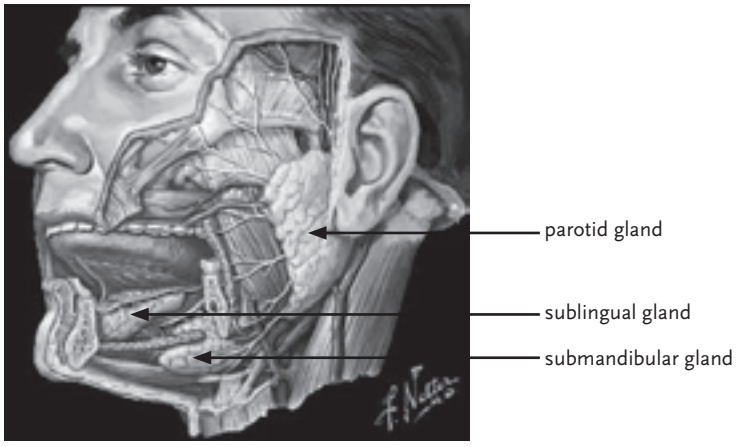
1.2. Anatomy and function of the salivary glands

Drooling and the treatment of drooling form the central theme in this study. The salivary glands are the targeted organ of the experimental intervention (Botulinum toxin injections) as well as the control intervention (scopolamine application). In the next section the functional anatomy of the salivary glands and the function of saliva are discussed.

1.2.1. The functional anatomy of the salivary glands

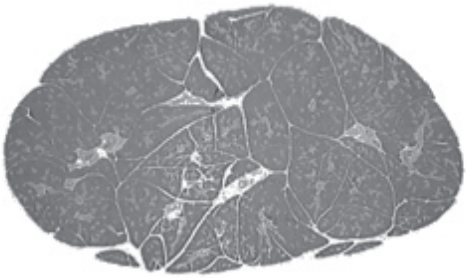
During early development the salivary glands arise as buds from the epithelial lining of the mouth; the parotid appears during the fourth week in the angle between the maxillary process and the mandibular arch; the submandibular (also called: submaxillar) gland appears in the sixth week, and the sublingual during the ninth week in the hollow between the tongue and the mandibular arch. The salivary glands are compound acinous glands, encased in a fibrous connective tissue capsule and grouped in three paired sets of large glands: the parotid-, submandibular-, and sublingual gland (Fig 1.2).

Figure 1.2: The location of the major salivary glands



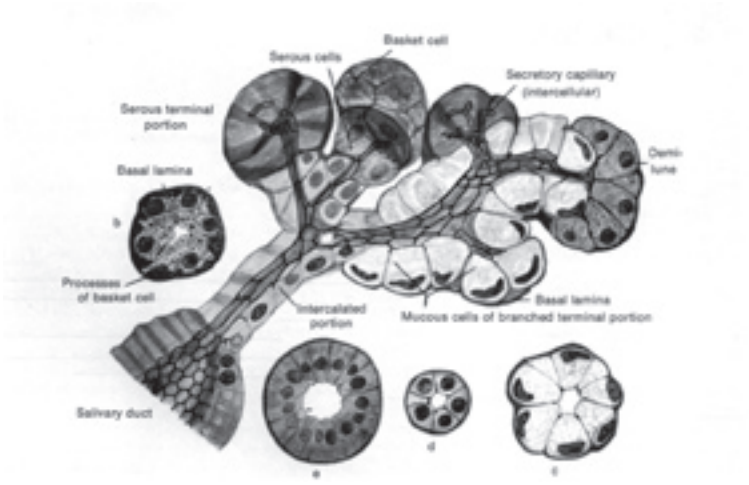
In addition, the mucous of the oral cavity (palate, lips, cheeks) and the tongue contains numerous minor salivary glands. The capsules of the salivary glands send septa into the substance of the glands, dividing them into lobules (Fig 1.3). The presence of a capsule and lobules is of significance in certain clinical situations or diagnostic and therapeutic procedures.

Figure 1.3: Macroscopic image of the submandibular gland



All glands of the oral cavity have a system of branching ducts (Fig 1.4). The secretory portions or acini of the pure mucous glands are usually long, branching tubulus. In the serous and mixed glands, the secretory portions vary from simple oval to tubulo-acinar forms with irregular outpockeings. The intra-lobular ducts are thin, branched tubulus called the intercalated ducts. Branches of the next larger order are the so-called striated ducts, also located in the interior of the smallest lobulus. The saliva is then collected in lobular and interlobular ducts and finally secreted through the larger primary or excretory ducts.

Figure 1.4: Reconstruction of a terminal portion of the submandibular gland



b, cross section of a purely serous terminal portion, showing basal lamina; c, cross section of a purely mucous terminal portion; d, cross section through as intercalated portion; e, cross section through a salivary duct.

The salivary glands may be classified in three categories (mucous, serous or mixed glands), according to the type of their secretory cells. Mucous cells elaborate a viscid secretion that consists almost exclusively of mucin. In glands with only serous cells, the secretion is a watery liquid that lacks mucus but contains, salts, proteins, and enzymes. The serous cells in the various oral glands have a similar microscopic structure even though they are not functionally identical. Some of them might be described as muco-serous. Mixed glands produce a viscid liquid that contains mucins, salts, and enzymes. The relative numbers of the two types of cells vary within wide limits.

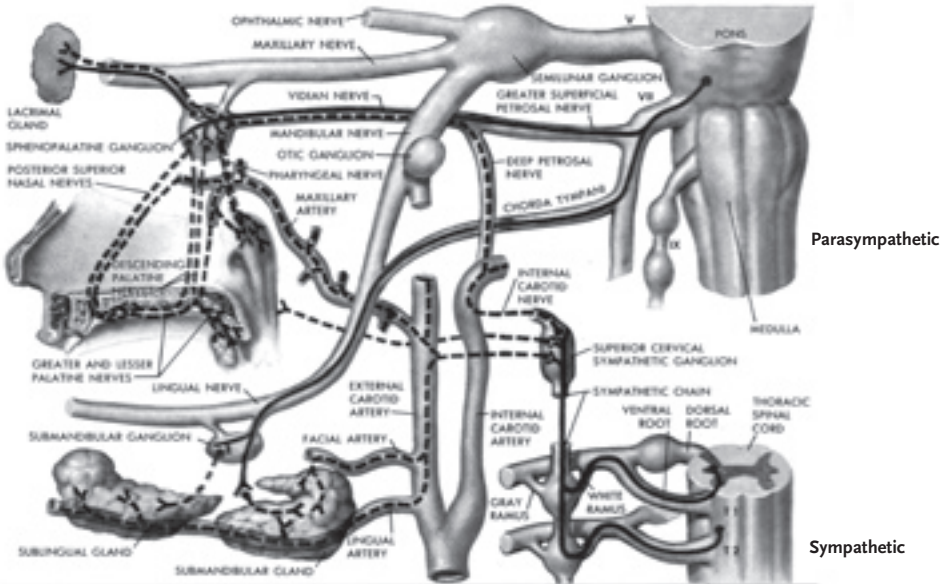
1.2.2. The neurological control of saliva secretion

Local reflexes of olfactory, gustatory and masticatory origin that stimulate the autonomous nerve system generate activation of the salivary glands. The salivary glands also secrete when mechanical, thermal, pain, or chemical stimuli act upon the nerve endings in the oral mucous membrane, or as the result of certain psychological stimuli. Distention of the gut and increased motility of the gut are also contributing factors. Tactile stimuli play an important role in the mouth, eliciting qualitative as well as quantitative modifications in secreted saliva. It is important to realize that the process of saliva secretion is of multifactorial origin, which can explain the continuous variation in production level.

The secretory function of the salivary glands serves under a complex higher neural control. Each salivary gland is provided with sensory afferent nerves. The salivary glands receive a dual autonomous supply: the parasympathetic and sympathetic nervous fibers. These two systems demonstrate less opposing action than was formerly thought. The secretory cells from serous and sero-mucous salivary glands can be stimulated by both sympathetic (α -adrenergic and β -adrenergic) and parasympathetic stimuli. On the contrary, mucous salivary glands are mainly stimulated parasympathetic.

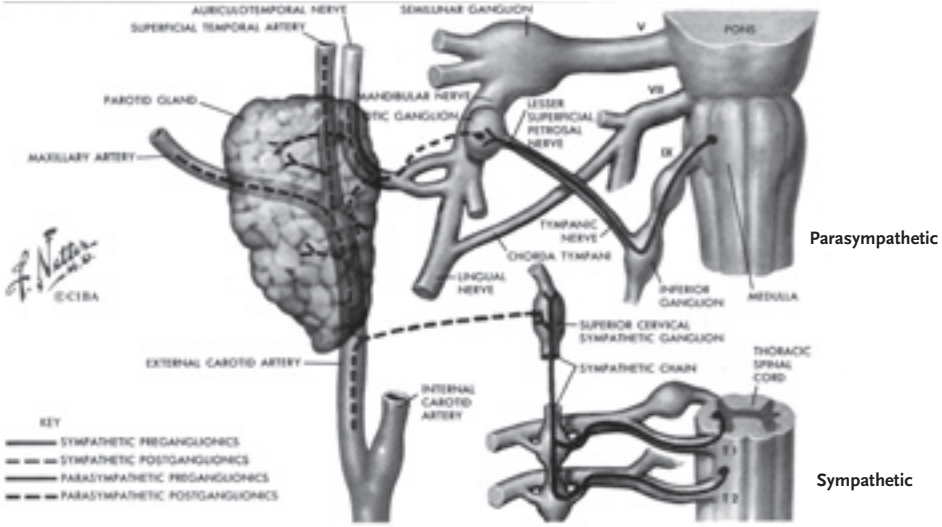
The parasympathetic stimuli (neurotransmitter: acethylcholine) to submandibular (submaxillary) and sublingual glands originate in the superior salivatory nucleus (Fig 1.5). The secretory nerve fibers decent a short distance through the glossopalatine nerve and than continue in the facial nerve (VII). They run through the chorda tympani branches of the facial nerve to the lingual nerve to end in the submandibular (submaxillary) ganglion from which the postganglionic fibers reach the submandibular glands as well as the sublingual glands.

Figure 1.5: Autonomic innervation of the mouth and pharynx



Parasympathetic nerve branches through the Facial nerve (VII) and sympathetic branches to the submandibular and sublingual glands. (From: The Ciba Collection of medical illustrations, volume 3, Frank H. Netter, M.D.)

Figure 1.6: Autonomic innervation of the mouth and pharynx



Parasympathetic branches through the Glossopharygeal nerve (IX) and sympathetic branches to the parotid gland (From: The Ciba Collection of medical illustrations, volume 3, Frank H. Netter, M.D.)

Parasympathetic stimuli to the parotid gland originate in the inferior salivatory nucleus and leave the brain via the glossopharyngeal nerve (IX) (Fig 1.6). They pass the tympanic plexus to continue in the small superficial petrosal nerve to end in the otic ganglion. The postganglionic nerve fibers are distributed to the parotid gland via the auriculotemporal nerve.

The sympathetic (neurotransmitter: nor-adrenaline) preganglionic fibers originate in the intermedio-lateral cell column of the first and second thoracic cord segments and go to the superior cervical sympathetic ganglion (Fig 1.5 and 1.6). Here the fibers effect synaptic connection with the postganglionic nerve fibers. The postganglionic sympathetic nerve fibers reach the parotid gland via a neural web, running with the external carotid artery and the middle menigeal artery, whereas the submandibular and sublingual glands are reached by fibers running along with the submental branches of the facial artery and the external maxillary artery.

Parasympathetic nerves provide the main drive for the secretion of fluid by the glands. Sympathetic impulses appear to evoke specialized responses that tend to modulate the composition of the saliva[45;46]. For example, stimulation of the parasympathetic nerves of the submandibular glands causes the secretion of abundant thin saliva, rich in water and salts but poor in organic substances. Stimulation of the sympathetic nerve, on the contrary, yields a small quantity of thick saliva, with a high content of organic substances.

It is a misconception that stress induced dryness of the mouth is due to sympathetic inhibitory fibers. This dryness originates from regulatory mechanisms in higher centers that inhibit salivary centers.

The preganglionic neurons of both the sympathetic and parasympathetic system as well as the postganglionic parasympathetic neurons secrete acethylcholine. The sympathetic postganglionic fibers secrete noradrenalin.

1.2.3. Saliva secretion

The parotid glands contain mainly serous acinar secretory cells. The submandibular glands are mixed, with the serous acini greatly outnumbering the mucous acini. The sublingual glands are also mixed but here the mucous elements predominate[47].

The speed of the secretory process through the ducts determines how much electrolytes are secreted.

The most important salivary electrolytes are Na^+, K^+, Cl^-, and HCO_3^- ions. The uptake from the blood serum forms an active process. Also Ca^{2+} and Mg^{2+} are present.

Proteins and glycoproteins are synthesized within the secretory cells[48]. In the pure mucous sublingual glands the cytoplasm contains mucigen, the antecedent of mucin. Each of the major salivary glands produces its own spectrum of proteins.

1.2.4. The function of saliva

Saliva composition is a major factor influencing the bacterial flora of the mouth and the formation of dental caries and plaque. Saliva helps to protect against tooth decay in several ways:

1. Saliva flow helps dilute and clear dietary sugars.
2. High pH (bicarbonate) buffers acids generated by bacterial fermentation.
3. Calcium and phosphorus supersaturation drives toward mineralization.
4. IgA from mucosal plasma cells is transcytosed into saliva.
5. Antimicrobial peptides and proteins, e.g. lysozyme and lactoferrin.

Saliva itself plays an important role in the preparation and digestion of the food offered to the mouth and in protecting the teeth and the oral soft tissues. The total secretion of saliva of the parotid, submandibular, sublingual, and the many buccal glands may be up to 1000 ml per day for adults. The production in especially young children will be substantially less.

Saliva contains essential substances: α-Amylase for the digestion of starches (parotid gland and submandibular gland), mucus for lubricating purposes (submandibular, sublingual, buccal glands), and ions like potassium, bicarbonate, sodium, and chloride. The pH of the saliva varies from 6.6 to 7.4, which is regarded as a favorable range for the optimal digestive action of α-Amylase.

The oral soft tissues are lubricated by the saliva, which makes phonation and good food passage possible. Swallowed saliva plays an important role in the defense against acid-induced esophageal mucosa injury, and against microbial infections.

Lubrication feels comfortable, as it is functional. The salivary mucins provide an effective barrier against environmental influences and they help to keep the tissues in a hydrated state[49].

The presence of nerve growth factor and epidermal growth factor in the submandibular saliva may accelerate wound healing.

Under basal conditions saliva of the mucous type is secreted in amounts of up to 0.5 ml/min. The majority of this volume comes from the submandibular, sublingual and buccal glands. This secretion plays an important role in maintaining oral tissue

healthy. The mouth is loaded with pathogenic bacteria that can easily destroy tissues and cause dental caries. However saliva helps to prevent deteriorating processes in several ways. The flow of saliva washes away the bacteria and the saliva contains enzymes and microbial proteins to destroy them.

1.3. Infantile Encephalopathy and Cerebral palsy

Different opinions exist on the definition of cerebral palsy. The following section describes the terms 'infantile encephalopathy' and 'cerebral palsy'. Although infantile encephalopathy is not a central issue of this thesis, it is described to distinguish it clearly from cerebral palsy. Cerebral palsy is described to delineate the definition that was adopted for this study.

1.3.1. Infantile Encephalopathy

Infantile encephalopathy (IE) is not a term used widely in clinical practice and it brings forward some basic misunderstandings because it lacks one strict definition. Infantile encephalopathy can be regarded as an umbrella term to describe all progressive, non-progressive, congenital or acquired cerebral lesions emerging in the developing brain early in life. The syndrome is clinically presenting with motor-, cognitive-, and perceptive impairments. One of the first physicians who used the term infantile encephalopathy was the English physician William John Little (1810-1894). He gave a historical lecture in 1861: 'On the influence of abnormal parturition, difficult labours, premature birth and asphyxia neonatorum on the mental and physical condition of the child, especially in relation to deformities'[50]. In addition, he stated that some of the clinical pictures were non-progressive disorders restricted to movement and posture that began in childhood. Other names that contributed to the description were Freud, Starr and the Sayre's (sr and jr). Freud was very pessimistic and wrote about infantile encephalopathy as a 'tragic chapter' in medical practice and supported the quotation by Starr:' ....a chronic disease incurable by medical treatment'. Some authors only used the term to describe "a diffuse disorder of the brain in which at least two of the following symptoms should be present: altered state of consciousness, altered cognition or personality, and seizures"[51]. By no means is infantile encephalopathy a classifying diagnosis as it covers a broad complex of symptoms.

1.3.2. Cerebral Palsy

Cerebral Palsy (CP) in fact means brain (cerebral) paralysis (palsy). As one of the first, W. Phelps used the term in 1937. He outlined a variety of types in detail based on topographical as well as physiological features. The work of several physicians resulted in a definition published by the Little Club in 1958:

'Cerebral palsy is a persistent though not unchanging disorder of movement and posture, appearing early in life and due to a non-progressive lesion of the brain, the result of the interference during its development'. Although the brain lesion remains the same, the resulting movement disorder may change, for either the better or the worse. A lot of variations on the theme have been proposed by several authors with among them: Pohl (1950), Denhoff (1951), Glidden Brooks (1956), Mc. Keith (1958), Bobath (1959), and Bax(1964).

Cerebral palsy can be referred to as a group of neurological disorders with impairment of motor function and loss of functional skills primarily caused by abnormalities in the pyramidal and extra-pyramidal tracts, resulting in a UMNS (upper motor neuron syndrome). A brain lesion will seldom selectively affect the motor areas. Several centers will usually be involved simultaneously, thus the picture will be that of a motor lesion combined with a variety of other defects, such as: mental retardation; epilepsy; visual and auditory disorders, etc.

The symptoms, present in the first year of life, may gradually improve and processes leading to the disappearance of cerebral palsy can continue after the first years of life[52;53].

A more recent consensus meeting in the early nineties of the last century brought up a revised definition of CP: 'an umbrella term covering a group of non-progressive, but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stages of its development'[54;55].

The term cerebral palsy according to this definition has been adopted in this study with the annotation that the clinical picture might be complicated by other symptoms and disorders and is not solely restricted to movement and posture. To meet this last point the term 'infantile encephalopathy' would be more correct because it encompasses the diversity of neurological syndromes; it leaves the possibility whether or not motor disorders dominate. According to international standards, however, the term CP will be used as a diagnostic entity.

Cerebral palsy is common and it affects 1.5 to 2.5 per live births in the United States and Australia[56;57]. More than 100.000 Americans less than 18 years of age have neurological

abnormalities attributed to cerebral palsy. Recently an epidemiological survey has been performed in the Netherlands. The calculated prevalence equaled 2.44 for the period 1986-1988[58]. As the result of a European collaboration project (Surveillance of Cerebral Palsy in Europe) a prevalence was found of 2.08 in the period 1980 - 1990[59].

In 1827 Cavauvieilh probably was the first to make a statement about the neuropathological origin of CP and mentioned cerebral hemi atrophy as the cause of hemiplegia. Since than several opinions and convictions have been reviewed with respect to the etiology of CP: cerebral sclerosis (Brissaud 1880), subdural hemorrhage (McNutt 1885), abnormal pregnancy, difficult labour and delivery, anoxia (Little, 1862), infections for example scarlet fever (von Heine 1860), chickenpox (Freud, 1891). Strumpell (1899) wrongly attributed cerebral palsy to a form of 'polio-encephalitis'. But he seems to have recognized clear pictures of CP resulting from different causes including para-infectious encephalopathy, cerebral embolism, or thrombosis.

Cerebral palsy is mainly caused by one of a variety of diseases and disturbances occurring during pregnancy, for example infections (rubella virus, cytomegalo virus, or toxoplasmosis), exposure to toxins, malformation of the brain, abnormalities in blood flow, genetic disorders, and complications of multiple birth. Cerebral palsy from such early causes is referred to as congenital and frequently related to preterm birth and low birth weight.

The majority of children afflicted do not acquire the condition from childhood injuries or diseases. Post neonatal events such as meningo-encephalitis, trauma, or occlusion of a cerebral artery or vein account for 12 to 21 % of all cases of CP[60;61]. Peri-natal events or intra-partum damage such as asphyxia, brain hemorrhage, or jaundice account for 3-12 % of all cases[62;63].

The incidence and prevalence of CP is not declining in spite of major improvements in obstetrical and perinatal care. The calculated CP prevalence rose significantly over time for the dutch situation: from 0.77 (1977-1979) to 2.44 (1986-1988). The survival of preterm and 'small for date' infants has added new problems to healthcare in the past decades. Beyond any doubt, CP, the spastic syndrome as well as extra pyramidal syndromes, and the consequent disabilities are part of these problems. The rate of CP in full-term infants with birth weights less than 1500 g appeared to be 25 to 30 times higher than among newborns weighing 2500g or more[64]. In an extended research program among pre-term infants with low birth weights in the Netherlands a 40 times higher risk was estimated (POPS: project on pre-term and small for gestational age infants, 1993)[65;66].

Thrombi-embolic processes during pregnancy seriously contribute to the risk for CP. The immature brain is vulnerable to non-traumatic intra-cranial hemorrhage, which develops in 40% of all newborn infants with a birth weight below 1500 gram.
From several studies it is clear that twin and higher-order multiple birth infants are at increased risk for CP[67;68]. In part, this is related to low birth weight frequently occurring in twins. However, normal birth weight twins also have a higher risk for CP than the normal population. Twinning, low birth weight, and premature delivery, although frequently related, appear to be separate factors increasing the risk for CP[69].
In a study by Minakami, twins conceived after ovarian induction, were followed[70]. The risk of an adverse outcome after 1 year including death, CP, and mental retardation was 2.8 times higher in monochorionic twins. A twin to twin transfusion syndrome might explain part of this problem[71].
Over the last decades assisted reproductive techniques together with ovarian induction have found their way to the regular medical practice. In particular woman of 35 years and older, and higher educated couples make use of these techniques. Between 1980 and 1993 in the United Kingdom, the twin pregnancy rate increased by 25% and the higher-order pregnancies more than doubled[72]. The risk for complications during pregnancy increases beyond the age of 35 and is even higher in cases of multiple gestations, for this age group. In-uteri death of one twin or a child of a higher-order pregnancy increases the risk of CP for the surviving child(ren) by more than 10-fold[67].
Taken the above mentioned points into account together with the problems still occurring at delivery there is little expectation that the incidence of CP will diminish in the next years. From this it seems certain that clinicians and other workers in the field of rehabilitation medicine will continue to be faced with the problems of CP in the near future.

1.4. Botulinum toxin and scopolamine

Intra-glandular injection with Botulinum Neuro Toxin Type-A (BoNT) is the experimental intervention evaluated in this study. The injections will be compared to a period of scopolamine application. Both, BoNT and scopolamine are discussed in the next section in order to provide basic background of the treatments.

1.4.1. Botulinum Toxin

The hypothesis of this study is based on the fact that injected BoNT leads to inhibition of cholinergic nerve endings. The seven identified toxin sero-types (A,B,C1,D,E,F and G) are anti-genitically distinct but also have a number of features in common: 1) they

are synthesized by the anaerobe Clostridium Botulinum bacteria, 2) and they all are of the same molecular weight (~ 150 kDa)[73]. Some authors rather distinguish an 8th subtype: C2 (Table 1.2).

Table 1.2: Botulinum Toxin Types, Target Sites, Discoverers, and Year Discovered

Type	Target	Discoverer	Year
A	SNAP-25	Landman	1904
B	VAMP	Ermengem	1897
C	Syntaxin	Bengston & Seldon	1922
D	VAMP	Robinson	1929
E	SNAP-25	Gunnison	1936
F	VAMP	Moller & Scheibel	1960
G	VAMP	Gimenez & Ciccarelli	1970

The complete gene sequences of the 'type A-Hall' strain Clostridium botulinum bacteria (Allergan), has been described. The reported sequence information for type A-Hall strain will potentially facilitate elucidation of the toxins interactions with the nontoxin proteins in the complex.

The toxin is synthesized as a relatively inactive single chain polypeptide. When acted upon by proteolitic enzymes this molecule is nicked to yield the fully active di-chain polypeptide composed of a heavy chain (H-chain) and a light chain (L-chain) linked together by a disulphide bond[73]. The mode of action for each of the sub-types is specific, all resulting in a well documented anticholinergic effect in the pre-synaptic nerve ending[74-76]. By far, the type-A neurotoxin (1296 amino acids) is the most frequently applied toxin for clinical use. In this study, BOTOX® (Allergan B.V., Nieuwegein, The Netherlands) was used; a type-A neurotoxin hemagglutinine/protein complex (900 kDa) of vacuum-dried purified toxin. Each vial contains 100 U (Units) corresponding with 5 Ng purified toxin type-A, also containing human serum albumin and sodium chloride. One unit of the toxin corresponds to the estimated median intra-peritoneal lethal dose (LD50%) in mice. These specific dosages are estimated by means of bioassays that are unique for each formulation. As a consequence the dosing scheme of different BoNT products cannot be straightforwardly compared*.

**The pharmaceutical form of BOTOX® is a powder which can be reconstituted with 0,9% NaCl. After reconstitution the attained solution can be used for 2 weeks provided it is kept in a refrigerator at approximately 2-8°C.*

BONT can enter the body from three sides of production: 1) by adsorption from the intestine, 2) by adsorption from a wound, or 3) by injection.
For clinical use the toxin should be injected into a target organ. After injection it will spread in the surrounding tissue by diffusion. The extent of this phenomenon depends on the injected volume and concentration of the toxin[77]. Within the parenchyma Botulinum toxin type-A, like the other sub-types, is capable of binding (Fig 1.7a) to the plasma membrane of cholinergic terminal nerve endings by the H-chain[78-81]. This process is irreversible. A process of internalization (Fig 1.7b) by endocytosis follows, in which the toxin enters the nerve cell encaged in a vesicle. Translocation (Fig 1.7c) occurs in which the toxin crosses the vesicle membrane and is released into the cytosol. The H-chain is mainly responsible for the binding and translocation processes. In this sense the H-chain is capable of targeting the L-chain precisely and selectively. On entering the cytoplasm the di-chained molecule splits.
The toxic activity is performed by the L-chain[82]. In case of the A subtype, the L-chain cleaves the SNAP-25 enzyme (synaptosomal-associated protein with a molecular weight 25 kDa): a cytoplasmatic protein that is located at the cell membrane of the terminal nerve ending and that is required for the release of the neurotransmitter acethylcholine. This is the process of blockage (Fig 1.7c). Functional restoration and reinnervation in realized by axonal sprouting (Fig 1.7d)
Under normal excitatory conditions, SNAP-25 is capable of linking to SNARE (soluble N-ethyl-maleimide sensitive factor attachment protein receptor) proteins within the cell membrane. Once the SNAP-25 protein is linked in the SNARE complex it is resistant to BoNT proteolysis[83].
Clostridial toxins are large proteins and they are immunogenic. Anti-BoNT antisera can prevent toxicity and provide recovery from botulism[84;85]. On the other hand these antibodies can diminish a therapeutic effect. Protective, neutralizing anti-BoNT antibodies are known[86-88]. However, also non-neutralizing antibodies, directed against the hemagglutinin protein of the complex, may be produced[89]. These antibodies do not influence the toxicity of the BoNT. Just a few patients develop anti-BoNT-A antibodies, particularly when large therapeutic doses of the toxin are injected. Patients who develop neutralizing antibodies to one BoNT serotype may benefit from other serotypes. For example, the application of BoNT-B, might be an alternative to overcome a therapeutic barrier from type A toxins[90].
Compared to the first release of pharmaceutical BoNT, Allergan has improved the product. The first form of toxin complex contained 25 ng whereas the present

Figure 1.7: Schematic presentation of the mode of action of Botulinum toxin-Type A

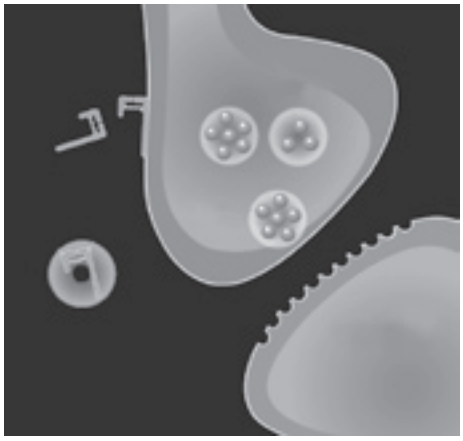


Figure 1.7a: After injection the heamag-glutinine-toxin complex diffuses though the parenchyma and binds to the plasma membrane by the toxin's heavy chain.

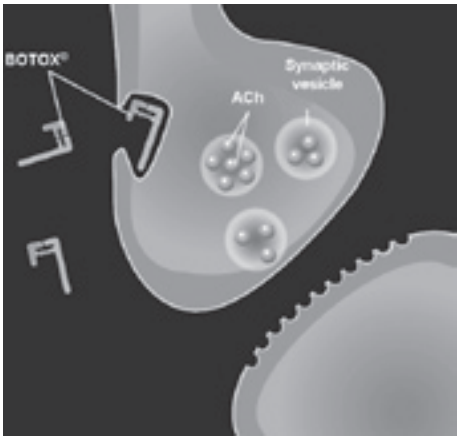


Figure 1.7b: The heavy chain induces a process of endocytosis. As a result the toxin is incorporated in the cytoplasm in a vesicle. The synaptic vesicles, containing Acethylcholine, still function properly.

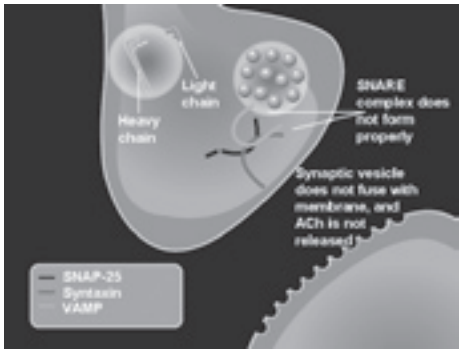


Figure 1.7c: After release into the cytosol the light chain binds to SNAP-25, which forms a blockage in the formation of the SNARE complex, preventing the excretion of Acethylcholine.

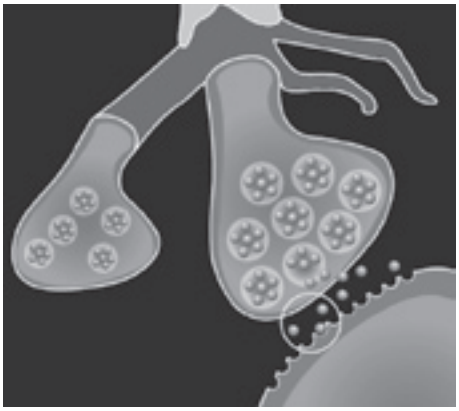


Figure 1.7d: The effect of BoNT is overcome by collateral sprouting and restoration of function at the neuro-glandular junction (indicated by circle).

formulation contains 5 ng of the toxin protein complex. In a study by Aoki it was found that the complex from the new bulk retains the same efficacy but elicit less immunogenicity[91;92].

1.4.2. Scopolamine

Scopolamine (hyoscine) is a belladonna alkaloid. Scopolamine, like atropine, is an antimuscarinic agent, which produces competitive antagonism of the actions of acetylcholine, which can be overcome with increasing concentrations of acetylcholine. Scopolamine, at usual dosages, produces CNS depression. However, excitement, restlessness, hallucinations, or delirium may paradoxically occur. In addition to its systemic anticholinergic effects, scopolamine is effective in motion sickness.

Using the transdermal system (1.5 mg) for topical application behind the ear scopolamine is well absorbed. The drug is thought to be almost completely metabolized in the liver and excreted in the urine. The duration of action of the transdermal system is up to 72 hours.

Hypersensitivity to scopolamine or to any ingredient in the formulation; pyloric obstruction; tachycardia secondary to cardiac insufficiency or thyrotoxicosis are contraindications for use. Caution to use is advised in patients taking drugs that act on the CNS as well as in patients with urinary bladder neck obstruction. Caution should be exercised when administering an anti-emetic drug or antimuscarinic drug to patients suspected of having intestinal obstruction (e.g., pyloric obstruction).

Adverse effects can be of different origin. Cardiovascular: bradycardia, tachycardia, hypotension. CNS: sedation, drowsiness; irritability, disorientation, hallucinations, impairment of memory and concentration, dizziness, confusion, acute toxic psychosis (resolves 24 to 36 hours after removal of the transdermal patch). Gastrointestinal: dry mouth; constipation. Ocular: blurred vision, dilated pupils. Dermatological: local irritation. Isolated cases of rashes and erythemas have been reported. Other: difficulty in urinating, rashes, erythemas.

1.5. Outline of the study

1.5.1. Primary objective

To evaluate the effect of Botulinum toxin on severe and socially disabling drooling in children with cerebral palsy.

1.5.2. Research questions

1. Does BoNT influence the submandibular salivary glands?
   * What effect does injected Botulinum toxin have on the salivary flow rate?
   * What is the proportional effect of Botulinum toxin injections (treatment intervention) on the salivary flow rate compared to scopolamine application (control intervention)?

2. Does drooling diminish if salivary flow rates are reduced?
   * What effect does intraglandular injected Botulinum toxin have on drooling?
3. Is quality of life influenced by the interventions?
   * Does a reduction of drooling change the individual's quality of Life
   * Does a reduction of drooling influence the practical efforts by family and caretakers in relation to drooling.

1.5.3. Patients

The inclusion of patients started in 2000, within nine months 53 patients were seen for intake. All subjects entered an intake period in which the diagnosis 'cerebral palsy' was confirmed. The inclusion criteria were tested (Table 1.3).
Eight children were not enrolled: the parents of three children choosed not to participate because of a long travel distance or the rather large number of study investigations that had to be fullfilled; five children were excluded because they did not satisfy the inclusion criteria.

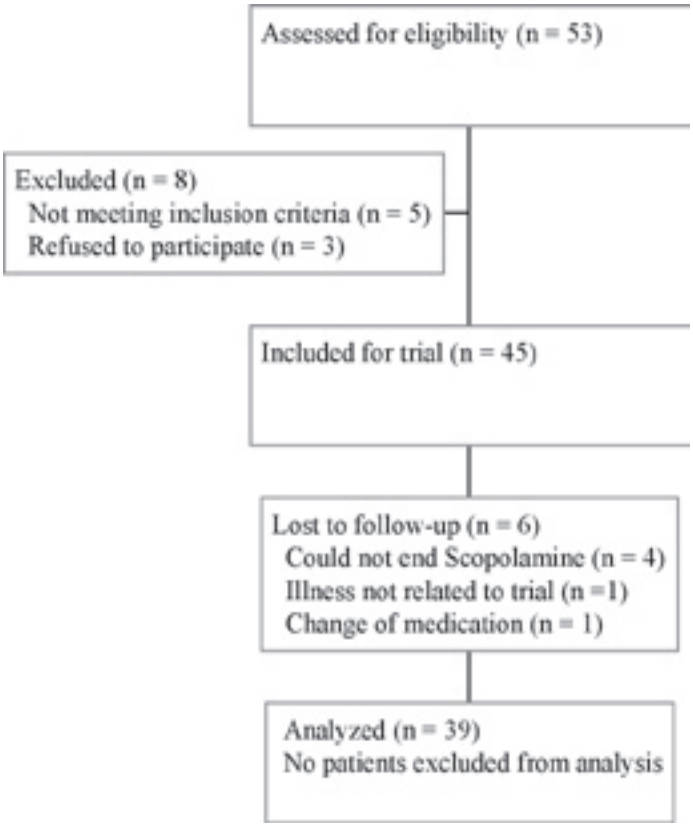
Table 1.3: Inclusion and Exclusion criteria

Inclusion criteria:
Children (male and female) of pre-school and school age (aging 3 – 18 yrs)
Confirmed diagnosis of cerebral palsy (clinical picture, CT, MRI, EEG)
A score of 3 or higher on the Teacher Drooling Scale, indicating severe drooling (chapter 8, table 8.1)
All medication, taken to treat drooling, stopped at least 3 months before start of the study
Minimal bodyweight 8 kg
Informed consent obtained
Caretakers have high enough cognitive ability to participate in the study
Readiness to participate for al least 8 months
Exclusion criteria:
The child is enrolled in another medical study
Previous surgical procedures in the oral or nasal cavity interfering with saliva production
Treatment with BoNT for another indication in the previous 6 months
Known hypersensitivity to Botox"or any part of the formulation
The use of drugs that interfere with saliva secretion
Known systemic diseases (bronchial asthma, congenital heart failure, and myasthenia gravis)

Thus 45 multiple complex handicapped children were included of whom 28 were male, 17 were female. The age ranged from 3 to 16 years with a mean of 9 yrs and 5 mo with a SD of 3 yrs and 7 mo.

None of the participating children suffered from complicating diseases. Nine of the patients had a medical history with recurrent pneumonia. No ENT surgery had been performed to treat drooling. Some of the children had received ear tubes, which was no contra-indication to participate. Of the initial population, 35 patients suffered from ante- and perinatal brain damage caused by preterm birth or asphyxia; 5 patients had a brain malformation; 2 suffered from post-infectious cerebral damage; 1 was known to have brain damage resulting from profuse epileptic seizures; 2 patients suffered from undefined retardation. Concomitant diseases comprised hypothyroidism in one patient, and colitis ulcerosa in another. Epilepsy occurred in 19 subjects 12 of whom used anti-epileptic drugs.

Figure 1.8:



The patients demonstrated the following motor disorder: 1 patient hypotonia; 27 spastic paresis; 17 mixed motor disorders with spastic and dyskinetic paresis. No patient exclusively showed athetosis or ataxia. Eight children were ambulant without aid and thirty-seven were (partially) wheelchairs bound.
Mental ability was determined for all patients based on available data at entry of the study. These data were collected from the institutions or schools that were attended by the children. Mental ability was scored on a 5 point scale according to the subdivision presented in table 1.4

Table 1.4: Scores of mental ability

	Level of developmental age	**Level of Intelligence quotient**
I	developmental age below 4 yrs	
II	developmental age 4 yrs to 6 yrs	IQ < 70
III	developmental age 4 yrs to 6 yrs	IQ _ 70
IV	developmental age 7 yrs or more	IQ < 70
V	developmental age 7 yrs or more	IQ _ 70

The following distribution of mental ability was found in the population: 'I' in 22 patients; 'II' in 9, 'III' in 2, 'IV' in 2, and 'V' in 10 patients.
Twenty-two children could not talk. None of the children attended a mainstream school. Twenty-nine went to special education schools and fourteen attended a daycare center for mentally retarded children.

1.5.4. Outline of the study

To treat drooling Botulinum Neuro Toxin Type-A (BoNT) has become in use over the past five years in children and adults with multiple complex neurological disorders. This PhD study was undertaken to provide scientific evidence for the effect of BoNT after injection in the salivary glands.
Drugs are widely used in the treatment of drooling. The anticholinergic drug scopolamine was chosen to serve as a reference for the effect of BoNT injections. The mode of action of anticholinergic agents can be understood from the fact that parasympathetic post-ganglionic stimulation of the salivary glands, mediated by acethylcholine, is completely blocked at the muscarinic receptors. A systematic review has been performed to find evidence for the efficacy of anticholinergic drugs to treat drooling, which is described in *chapter 2*.

In order to obtain reference data on saliva secretion a study was performed in healthy children. The results are described in *chapter 3*.
The collection of saliva from the mouth is difficult and subjected to bias especially in the investigation of children with severe handicaps. As described in the literature, the swab method has been used for investigations in healthy subjects. *Chapter 4* describes the measurement of the salivary flow rate by the swab method in handicapped children. The quantification of the measurement error and biological variation are described.
The treatment of drooling by BoNT is a new challenge. As a prerequisite to start the present study, the injection technique for the salivary glands had to be safe and easy to perform. A pilot study was undertaken in order to evaluate the injection technique in sufficient detail, which is described in *chapter 5*.
In *chapter 6* the first experiences with intra-glandular BoNT injections are presented, based on a case series.
The core of this thesis is described in the *chapter 7 and 8*. A detailed description of the physiological effect of scopolamine and BoNT on the secretory function of the salivary glands is described in *chapter 7*. The clinical relevance of the treatment modalities is outlined in *chapter 8*.
As mentioned in the introduction 'anterior drooling' should be distinguished from 'posterior drooling'. A case study is presented in *chapter 9* to describe the effect of BoNT injections on posterior drooling. The consequences for some aspects of quality of life are described in *chapter 10*.
Chapter 11 provides the 'general discussion'.

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Chapter 2

A systematic review for evidence of efficacy of anticholinergic drugs to treat drooling

Arch.Dis.Child 2003;88:911-4.

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Abstract

Objective: Drooling frequently occurs in children with multiple handicaps. The application of anticholinergic drugs is regarded as a potential strategy to treat drooling. The literature was studied to investigate the efficacy of anticholinergic drugs.

Design: A systematic review of the medical literature has been performed.

Setting: The study is part of a larger program investigating new options for the treatment of drooling, approved by the medial ethics committee of the University Hospital.

Intervention: A computer-aided search of original studies concerning the treatment of drooling has been carried out. According to the rules of systematic reviews the methodological and statistical integrity of the identified studies were assessed with priori defined criteria. The articles were weighed for their separate contribution to the evidence synthesis.

Results: The search resulted in 64 reports of which 7 studies passed the screening and were subjected to further assessment and discussion by three referees. Because of the small number of reports and the methodological restriction within the studies, no meta-analysis could be performed.

Conclusion: No general conclusion can be made about the efficacy or average effect of anticholinergic drugs to treat drooling in children with multiple handicaps. There is some evidence that 3 anticholinergic drugs (Benztropine, glycopyrrolate, and Benzhexol hydrochloride) are effective in the treatment of drooling but it cannot be concluded that one drug is preferable.

Introduction

Drooling is a normal clinical manifestation of the growing child, but if it lasts after four years of age it is abnormal[1-3]. As noted in many articles, drooling occurs frequently in children with Cerebral Palsy (CP). There is rarely hypersalivation[4] and drooling rather is the result of a defect in the oral phase of swallowing5. A lack of control in the coordinate mechanism of oro-facial, palato-lingual, and head-neck musculature leads to an excessive pooling of saliva in the anterior mouth[3]. Other factors such as spasticity or a decreased intra-oral tactile sensitivity predispose to drooling.

Drooling children frequently have a chronically irritated skin over the chin and the peri-oral region. In cool weather the dampness from saliva is chilling. The pooling of saliva in the oral cavity increases the risk of aspiration particularly in combination with gastro-esophageal reflux. There may be chronic loss of fluid and nutrients.

Drooling is cosmetically unappealing and has a negative social effect that can be

detrimental to the emotional and behavioral development of the individual. The unsightly nature of the drooling and salivary spray when the child talks, sneezes or coughs can result in a degree of alienation[6]. Patients who are aware of the problem are less likely to interact with other children during normal peer activities. Drooling has been reported to be a significant problem in about 10% to 37,5% of patients with cerebral palsy[2;7;8]. Bachrach[9] interviewed parents by means of a questionnaire that included questions regarding drooling. Thirty-four percent indicated it was sometimes, and 16% responded that it was often a problem. Caretakers often spend much time in suctioning and cleaning the children's mouths and changing their clothes. Attempts to reduce drooling have included both invasive and non-invasive techniques[10]. The latter refers to behavioral techniques, speech therapy, oral sensory and motor training, orthodontic treatment[1;12], anticholinergic drugs[9;13-21], and (intra-ductal) radiation[22;23]. Surgical procedures include salivary gland excision[24], salivary duct rerouting[2;21;24-27] or a combination of these. Chordatympanic neurectomy has been performed to eliminate parasympathetic stimulation to the salivary gland[28]. The application of anticholinergic is regarded as a realistic possibility to treat drooling and many physicians are exploring the effect of these agents along with the prescription of physiotherapy and speech therapy, as the first choice of treatment[9;11;13;14;16-20;29-32]. In a narritive review of the literature Nunn[10] concludes that "the lack of a scientific approach to many of the studies cited makes it virtually impossible to conclude that any one approach is better than another".

The objective of this study is to perform a systematic review of the literature to investigate the efficacy of anticholinergic drugs to treat drooling in children with multiple handicaps.

Material and methods

Search

Material for the review (articles about relevant studies published before June 2002) were identified by a systematic search in the bibliographic databases of Medline (from 1966), Pubmed (from 1966), the Cochrane Library, and Current Contents (from 1996) using the keywords shown in table 2.1. The keyword "anticholinergic drug" appeared to be inadequate, because the studies in which the generic name for a specific drug was used would be excluded. The keywords were expanded by using the "explode function" present in Medline. References from the retrieved articles were checked. The retrieved articles were screened by title. If any uncertainty remained, printouts of the abstracts were checked.

Table 2.1: The applied keywords for the literature search

Groups Keywords	Pharmacological preparations	Symptoms	Treatment	Population
1.	Anticholinergic drug	Drooling	Treatment	Child
2.	Anticholinergic drugs	Drool*	Treatments	Children
3.	Anticholinergic drug*	Hypersalivation	Treatment*	Child*
4.	Anticholinergic medication	Hypersal*	Intervention	Infant
5.	Anticholinergic treatment	Dribbling	Interventions	Infants
6.	Anticholinergic treatments	Dribb*	Intervention*	Infant*
7.	Anticholinergic treatment*	Sialorrhea	Management	Pre?school Child
8.	Cholinergic blocking	Sialor*	Management*	Preschool Children
9.	Cholinergic blockings	Ptyalism	Therapy	Pre?school Child*
10.	Cholinergic blocking*	Ptyal*	Therapy*	Adolescence
11.	Cholinergic antagonist	Saliva		Pediatric patient
12.	Cholinergic antagonists	Saliv*		Pediatric patients
13.	Cholinergic antagonist*	High salivary secretion		Pediatric patient*
14.	Choline?asterase inhibitor	High salivary secretion		Juvenile
15.	Choline?asterase inhibitors	Salivation		Juveniles
16.	Choline?asterase inhibitor*	Salivary flow		Juvenil*
17.	Parasympaticolitics			
18.	Parasympaticolitica			
19.	Anti?muscarinic			
20.	Scopolamine			
21.	Scopoderm TTS			
22.	Hyosine			
23.	N-Methylscopolamine			
24.	Butylscopolammonium bromide			
25.	Benztropine			
26.	Glycopyrrolate			
27.	Atropine			
28.	Pyridostigmine			
29.	Benhexolhydrochloride			
30.	Antisialorrhoic			

Only patient related studies aimed at the treatment of drooling with anticholinergic drugs in multiple handicapped children and published in the English, German, Dutch, or French languages were included. Letters, abstract and 'published presentations' were excluded.

Table 2.2: Definitions and criteria for selection and inclusion of articles in the study

Definitions
* Child: a person up to the age of eighteen
* Drooling: "The unintentional loss of saliva from the oral cavity due to pyramidal or extra-pyramidal impairment"
Criteria for inclusion of selected articles
* The study is patient related and aimed at the treatment of drooling with drugs
* The study has been performed as a clinical trial, cohort study, case series, case-references or case-control study
* The study population or relevant subgroup primarily concerns children of pre-school and school age
* The treatment of drooling has been evaluated with descriptions of the population (diagnosis and an indication of impairment and disability), the intervention and the outcome measure
* Published in the English, German, Dutch or French languages
Criteria for exclusion of selected articles
* Articles written in other languages that only provided an abstract in English
* Letters, abstract and published presentations without acceptable description of methodology, population and results
* Narrative reviews

Table 2.2 provides the definitions and the exact inclusion and exclusion criteria for the articles. Three referees (PJ, PvT and JvL) independently analyzed all selected studies. The publications were blinded with respect to author, source and results. Subsequently the level of methodological quality was assessed. The studies that passed the preliminary screening were subjected to a systematic review using a checklist with priori defined methodological criteria. The checklist (Table 2.3) was constructed according to a system, originally developed for the evaluation of randomized controlled clinical trials (RCT's)[33-36].

Each criterion for internal validity (V1 - V7), external validity (V8 - V15) and the method

of data presentation (D1 - D5) was assessed and scored with a three level system: [3] sufficient, [2] moderate, [1] insufficient. In case a choice had to be made between sub-items, only one of these could be filled in and the other sub-item was scored [0].

Table 2.3: Checklist for methodological evaluation of included articles

Internal validity (V1 -V7)	
1	Randomization method presented
2a	Homogeneity of the population at entry of the study concerning diagnosis, confounding factors, prognostic factors
2b	Sub-group analysis done with respect to the mechanism for drooling if necessary
3	Description of a method to control for 'adherence to therapy'
4	Description of a system for control of co-interventions (E.N.T.-surgery, behavioral therapy and medication) at entry and during the study
5	Standardized method of outcome measure fully described
6	Repeated measurements during the observation period according to a fixed protocol
7	Intention-to-treat analysis if applicable
External validity (V8 - V15)	
8	Description of inclusion and exclusion criteria
9	Accurate description of the planned therapy or interventions
10	Check for co-intervention during the trial
11	Outcome rates correctly listed in the text
12	Description of relevant characteristics related to loss to follow-up and adequate management of dropouts
13	Presentation of the number of subjects 'loss to follow-up'
14	Minimal follow-up period of 3 months
15	Control for side effects
Data Presentation (D1 - D5)	
1	Adequate sample size
2	Presentation of the mean of the outcome measures
3	Presentation of the standard deviation of the outcome measures
4	Method of statistical analysis described in relation to the design used
5	Appropriate statistical analysis done

This system implies a maximum sum score of 60 points for the 20 items on the checklist. However, some items were not applicable [NA] in view of the specific study design. In such a case the maximum sum score decreased accordingly.

Internal validity

Randomization (V1) is a critical issue. The description of how randomization was achieved had to be made clear. It was not possible to verify whether the randomization procedure was actually properly executed as this is hardly ever mentioned in published work.

The homogeneity (V2) of the study population has been assessed. The item on homogeneity is subdivided into two sub-items (V2a and V2b). These items evaluate the comparability of the subjects within the population with respect to the underlying mechanism of drooling; it ought to be reflected in homogeneity for diagnosis and the resultant motor impairment. This item also investigates the homogeneity of the population under study with respect to confounding factors at entry of the study (age, stage of the disease, co-morbidity, and co-medication) that could influence salivary flow. In particular concurrent use of anticholinergic medication as well as caries, and peridontologic disturbances is of importance. A [3] was assigned if the population was well documented. In case incomplete data had been given a [2] was scored. In cases there was insufficient information to determine the degree of homogeneity; a [1] was scored. A V2a score of [2] or [3] satisfied the minimum requirements for homogeneity. Consequently sub-group analysis was not needed for this study and item V2b was scored as [0]. If V2a had a score of [1], sub-group analysis had to be performed. In case subgroup analysis had been carried out, the score for item V2a was transformed to [0].

Adherence to therapy (V3) had to be measured and indicated in the description of the study. Control for relevant intervention at entry and during the trial (V4) had to be described and to be controlled (i.e. surgery in the oral cavity, behavioral therapy and the application of medication aimed at reducing drooling).

A quantitative indication of the severity of drooling was always required. The accuracy of the applied severity or frequency scoring system was evaluated (V5). A quantitative score or ratio-scale provided in absolute numbers (e.g. ml/min) was judged sufficient and consequently scored[3]. Semi-quantitative scores that used an ordinal scale such as the Teacher Drooling Scale[37] are classified as moderate [2]. The use of dichotomous scales was considered to be insufficient [1]. Outcome measurements had to be repeated

at fixed intervals during a relevant period after start of the intervention (V6).
Randomized clinical trials had to meet the intention-to-treat principle (V7).

External validity
The description of inclusion and exclusion criteria for subjects (V8) in a study was considered to be essential. A thorough description of the planned therapy (V9) was obligatory. This item scored sufficient if a description was given. Co-interventions during the trial (V10) had to be described and the relevance with respect to the therapy had to be mentioned. The outcome measures such as ratio scales or the results of ordinary scales had to be described in the text (V11). In case the description was unclear or provided no meaningful information, this item was regarded as insufficient.
The reasons for 'lost to follow-up' (V12) had to be given, and these cases needed to be managed adequately. This item also scored positive in case there were no dropouts during the study or if the description of the dropouts contained convincing arguments. The absolute number or the percentage of subjects 'lost to follow-up' (V13) needed to be mentioned. Based on the information provided, it was demanded that the percentage of lost to follow up could be calculated.
The follow-up period had to be long enough (V14) to determine the usefulness of the anticholinergic drug treatment and possible side effects. This period was determined to be a minimum period of 8 weeks since it could be expected that side-effect would be clear by that time. Side-effects of the therapy (V15) were regarded as a critical success factor. This criterion tested whether there had been sufficient control for side effects.

Data presentation
The number of patients was judged in relation to the study design (D1). Outcome measurements had to be adequately reported with quantitative measures (absolute numbers or relative difference scores) with presentation of the Mean (D2) and Standard Deviation (D3).
The planned statistical analysis had to be described clearly in relation to the proposed research design (D4), and the article had to provide evidence the statistical analysis had indeed been conducted (D5).

Results of the literature search

The primary search resulted in 64 articles. Of these retrieved articles 36 were excluded based on the contents of the abstract; 30 articles appeared to be irrelevant in relation to

the research questions of this review[26;38-66]. Two titles were listed twice in the primary search[40;57].These duplicates were removed. One Japanese article was excluded[67], as were 2 articles concerning 'case reports[19;68], and 1 narrative review1. The remaining 28 articles were completely read. Seventeen articles without abstracts were rejected from the study because they were not relevant to the research questions[25;69-84]. One article was recognized as another narrative review[31] and was excluded. Two articles did not concern children or problems related to CP[29;32]. One study had a retrospective design and was excluded[9]. Screening of the references of all articles did not bring up new articles.

Sixty-four articles were retrieved in the primary search from which seven articles could be selected for further investigation.

The methodological quality of the seven selected articles was determined (Table 2.4). Three studies were randomized clinical trials (RCT)[11;14;17], 3 were cohort studies[13;18;20] and 1 had an experimental design[30].

In this review one RCT[14], one study with a classical Virchow design30 and one cohort study[18] were judged as methodologically adequate in relation to the study design that was used. Two RCT[17;11] and 2 cohort studies[13;20] did not meet the proposed methodological criteria. In order to provide a complete overview of the available literature, these articles are also listed in table 2.4.

For the methodological quality of the selected RCT's the internal validity (table 4) was regarded as the most critical aspect, in particular homogeneity (V2). Randomization (V1), the 'Intention-to treat analysis' (V7), adherence to treatment (V3) and, the method of outcome measure (V5) were weighed as equally essential. Randomization and Intention-to-treat are items that are not applicable for cohort studies. To be qualified as an article with good internal validity, the studies had to satisfy the above mentioned criteria of internal validity with a minimum score of 12 points (out of 21) for RCT's or 8 points (out of 15) for cohort studies. The outcomes of the items on internal validity, external validity and data-presentation are listed in Table 2.4.

Three referees analyzed the selected articles. The scores for the methodological and statistical items were scored on prepared lists. Consensus about particular items was acquired by a thorough discussion. It has not been necessary to consult an other referee.

Table 2.4: The methodological assessment of selected studies

Author and year of publication	Blasco	Camp-Bruno	Lewis	Mier	Reddihough	Stern	Owen
	1996[13]	1989[14]	1994[17]	2000[11]	1990[18]	1997[20]	1992[30]
Research design	Cohort study	RCT	RCT	RCT	Cohort study	Cohort study	Experiment
Maximum possible sum-score	54	60	60	60	54	54	60
Internal Validity	*Scores (minimally required score for specific item)*						
1 Randomization	NA	3(2)	2(2)	1(2)	NA	NA	3(2)
2a Homogeneity of the population	2(3)	3(2)	0(2)	3(2)	3(3)	3(3)	2(2)
2b Sub-group analysis	0(3)	0(2)	2(2)	0(3)	0(3)	0(3)	0(2)
3 Adherence to therapy	1(3)	3(3)	1(3)	1(3)	1(3)	3(3)	1(3)
4 Co-intervention control system	1	3	1	1	1	1	1
5 Standardized outcome measure	1(2)	2(2)	2(2)	2(2)	3(2)	2(2)	2(2)
6 Repeated measurements	1	3	3	3	2	1	3
7 Intention to treat	NA	1(3)	1(3)	1	NA	NA	0(3)
External Validity							
8 In/Exclusion criteria	3(3)	3(3)	3(3)	1	3(3)	1(3)	1(3)
9 Description of intervention	3(3)	3(3)	3(3)	3(3)	3(3)	3(3)	3(3)
10 Co-intervention checked	3	1	1	1	1	3	1
11 Outcome rates listed in text	1(3)	3(3)	3(3)	3(3)	3(3)	1(3)	3(3)
12 Description and management of lost to follow-up	3(3)	3(3)	3(3)	3(3)	1(3)	3(3)	1(3)
13 Number of lost to follow-up	3(3)	3(3)	3(3)	3(3)	1(3)	3(3)	1(3)
14 Follow-up period	3	1	1	3	3	2	3
15 Side effects	3	3	2	3	3	3	3
Data presentation							
1 Adequate sample size	3(3)	3(3)	3(3)	3(3)	3(3)	3(3)	1(3)
2 Mean	1(3)	3(3)	1(3)	3(3)	3(3)	1(3)	1(3)
3 Standard Deviation	1(3)	3(3)	1(3)	3(3)	3(3)	1(3)	1(3)
4 Statistical method	1	3	1	3	3	3	3
5 Statistical analysis performed	1	3	3	3	3	3	3

In the next section the separate articles are described with respect to the methodological quality and, the clinical relevance of the presented information.

Camp-Bruno et al[14] investigated the effect of Benztropine for the treatment of drooling in 27 subjects in a placebo controlled RCT. The scoring method of the severity and frequency of drooling was outlined in detail. Homogeneity of the population was rated insufficient because there has been no correction for age, while in the literature an influence of age until puberty on salivary flow has been described. Subgroup analysis was not performed. Control for adherence to therapy was considered sufficient. The criterion of the "intention to treat" principle was not satisfied. Of the 27 patients 7 were later dropouts. In the opinion of the reviewers a percentage of 30% dropouts was too large. The adverse effects of three patients were described, data of the other four missed. The adverse effects were scored on an ordinal scale. Unfortunately the outcomes of the measurements were not presented. The internal validity of the study was good: 85,7% (18/21, meaning 18 out of a maximum of 21 points), although the "intention to treat" principal was not satisfied. The external validity was good: 83,3% (20/24), as was the way in which the data were presented: 100% (15/15). In conclusion this study could be used for the evidence synthesis.

The study by Bruno-Camp shows that in principal Benztropine can have a positive effect on drooling. On the other hand, one cannot make a statement about the average effect of the drug. During the study the population with 27 subjects was too small to compensate for a dropout percentage of almost 30%. Three of the 7 dropouts were certainly related to the treatment. With the results presented the question whether non-therapy related circumstances have influenced the outcome remains unanswered. A statement about the treatment and its adverse effect cannot be made because the study has a follow-up period of a few weeks.

Mier et al[11] performed a double-blind, cross-over study to evaluate the efficacy and dose-ranging of glycopyrrolate to treat drooling. For this purpose thirty nine children were enrolled. Randomization was not described and no information was given about the inclusion and exclusion criteria of the subjects. There was insufficient homogeneity in the population because there has been no correction for age. Sufficient information has been given about the mechanism of drooling, other medical conditions and, adherence to therapy. The criterion of the "intention to treat" principle was not satisfied. The scoring method of the severity and frequency of drooling was outlined in detail. Two dosage regimes for glycopyrrolate were used and sufficiently described. The results were presented in a clear way and sufficient statistical information has been

provided. Referring to the chosen design the number of patients included is enough to require adequate statistical power. The number of drop-outs (31%) is not acceptable. This seriously reduces the methodological value of the study in particular because the drop-outs appeared to be selectively related to the medication, together with the fact that the intention-to-treat principle was not satisfied. The score on internal validity was low to moderate: 52.3%, due to insufficient description of randomization and the study population. External validity scored 83,3% (20/24) and data presentation 100% (15/15). Because of the score on internal validity this study could be used in the evidence synthesis to support primary evidence.

The authors conclude that children tolerating glycopyrrolate will demonstrate "marked improvement in drooling" at individual doses. Dosage guidelines are provided. In 20% of the cases adverse effects necessitated withdrawal of the glycopyrrolate.

Lewis et al[17], investigated the effect on drooling of a trans-dermal application of scopolamine, in a placebo controlled RCT with a crossover design. A two-week period of scolamine was plotted against the same duration of placebo treatment. The homogeneity of the population was insufficient and no adequate subgroup analysis was carried out. The adherence to therapy was not described and the method of measurements insufficiently described. A five-level scale was used in which the amount of present drooling during therapy was compared to the usual situation for the particular patient. In this respect the patient was supposed to serve as his or her own control. The method was regarded as being insufficient because it was unclear how many people finally observed a particular child and in which way data were calculated. The "intention to treat" principal was not satisfied. Side effects were well documented. The method of statistical analysis was described in relation to the design used, but the analysis itself was not presented in sufficient detail. For example no means and standard deviations could be calculated.

Internal validity of this study was moderate: 57,1% (12/21). External validity scored 79,2% (19/24) and data presentation 60% (9/15). The article could not be used in the evidence synthesis because of the low internal validity in combination with the way data were presented.

The authors present a good overview of the possible side effect of scopolamine: pupil dilatation, dizziness, pruritus around the patch and, increased mouthing behaviors. One child experienced deterioration of a pre-existent refractory seizure disorder.

Owen et al[30] investigated the effect of Benztropine on the salivary flow using the classical Virchow Design: a-b-a-b. Three patients were enrolled in this study. Salivary

flow was scored using an ordinal scale. A baseline period was introduced followed by a period of optimal dose finding. After a washout period the patient received medication or placebo (within-subject design). Using this design, follow-up was not required because it was not relevant in relation to the research question. The methodological quality of the study was correct. The a-b-a-b design in this case could only answer the question whether the salivary glands react to the application of Benztropine. From the results presented, one can conclude that the inter-individual variation was rather large. A general conclusion for a population could not be drawn because of the small number of patients. The study does not permit a judgment as to whether Benztropine is a useful therapy in the treatment of drooling in children with CP, in general. There was insufficient homogeneity in the population due to the great variation in age of the three participants. Subgroup analysis was not conducted although the diagnosis and potential confounders were mentioned, but in the discussion of the results these data were not related to a specific patient. Because of the chosen design, it was methodologically inadequate not to mention co-interventions. The performance of statistical analysis was insufficient since no information was given as to whether analysis was actually done. No results were reported. The internal validity score was moderate: 57,1% (12/21). The score on external validity was moderate: 66,6% (16/24) and more attention should have been paid to the data presentation: 60% (9/15). Because of the objective and the chosen research design this study could only be used as additional information to support the evidence.

The study by Owen indicates that the salivary glands would react to Benztropine with a positive effect on salivary flow. With the limited subjects included and the chosen research design, no conclusion can be made about the average effect of the drug in a certain population.

Reddihough[18] studied the effect of Benzhexol Hydrochloride (Artane) on drooling. During 3 months, 20 children 3 to 12 years of age were treated. The outcome measure was described in detail and well standardized. The authors provided the reader with a good indication how drooling was defined during the observations in a well-documented homogeneic population. Some criticism could be addressed to the wide spread in age of the participating subjects. Control for the adherence to therapy and co-intervention was insufficient. Inclusion and exclusion criteria were sufficiently described, as was the intervention. The outcome measures were listed in the text unfortunately as a description for the population as a whole. From the presented table with results, one could not conclude which data belonged to a particular patient. This might have

been of importance with respect to the differences in age. Results were presented as percentages of the median score of drooling before and during treatment. Statistical procedures were clearly presented. The score on internal validity was moderate: 66,6% (10/15) and external validity good: 75% (18/24). Data presentation scored 100% (15/15). The study by Reddihough, a cohort study, only provides additional information to support the evidence. In the evidence synthesis this study could be used as secondary evidence.

Following good clinical practice the problem of drooling is outlined together with the remark that 'salivary flow is profuse in infancy, but decreases rapidly up to five years and then more gradually to puberty'. The article gives adequate information about the application of Benzhexol Hydrochloride and description of how the optimal dosage was achieved. No relation was found between the dosage and the age of the child. Drooling decreased in 17 out of 20 subjects. Because the study was of reasonable methodological quality, two conclusions are likely: a) Benzhexol Hydrochloride has a good effect on drooling, although the average effect remains unclear, b) the optimal dosage varies from 2x2mg up to 2x3 mg daily.

Blasco et al[13] investigated the effect of Glycopyrrolate as a treatment for drooling in 40 children. This was a cohort study that did not satisfy the minimal requirements for internal validity. The data about the homogeneity of the population were incomplete, no information was provided about potential confounding factors such as age, stage of the disease, co-morbidity, inflammation, and caries. The use of medication was made explicit and half of the population appeared to use a variety of drugs but no appropriate information was given as to whether these drugs could influence salivary flow. Adherence to therapy was not indicated, and the method of outcome measures was graded as insufficient since a dichotomous scale was used. All items for external validity but one were scored positive, unfortunately the outcome measures were not listed in the text. In the data presentation baseline measures were not mentioned. Internal validity scored low 40% (6/15), external validity 91,6% (22/24) and, data presentation 45,6% (7/15). Based on the data set presented in the article, together with the scores on internal validity no statement could be made about the efficacy of Glycopyrrolate on drooling.

Although this study cannot be used in the evidence synthesis, the information provided is of clinical importance. A short overview of the problem of drooling and the treatment possibilities were given. The use of anticholinergic drugs and in particular the dosages of Glycopyrrolate were presented. This is in line with the opening sentence of the

article in which the author stated that the objective of the study was to outline 'the use of glycopyrrolate in the control of drooling in children and young adults with CP and related neurodevelopmental disabilities'.
In the study by *Stern*[20] the effect of Glycopyrrolate to treat drooling was investigated in a population of 24 subjects. Although the mean age of the participants is given, it is not possible to determine whether more than 50 % of the population is under the age of eighteen. The outcome measures used have limitations. Parents were asked to complete a questionnaire 'some time after the end of the trial' in order to assess the effect of Glycopyrrolate. This uncertain time interval violated the quality of internal validity. The authors admit that the way, in which the questionnaires were completed, is open to discussion and criticism. Adherence to therapy was not described. The items on the inclusion and exclusion criteria, homogeneity and the performed intervention were satisfied. The number of lost to follow-up was not indicated. The measurements before the start of the therapy were not listed in the text nor were the post treatment results given per patient. Insufficient insight was acquired in the effect of the intervention with Glycopyrrolate. Information about statistical analysis provided in the text was inadequate. Internal validity scored moderate: 66% (10/15), external validity: 75% (18/24) and, data presentation: 73,3% (11/15). As a case series the study could not be taken into account for 'evidence synthesis'.
From a clinical point of view the authors provide a good overview of the mechanism of drooling in general and the treatment possibilities, even though this was not the purpose of the article.

Evidence synthesis and discussion

Evidence synthesis

RCT's can be considered to give primary evidence where-as cohort studies, referred to as pre-experimental design, can only provide additional information to support the outcome of the RCT's. We performed an in-depth review of the medical literature in order to do a meta-analysis. Unfortunately only seven studies could be identified. In our review, articles subjected to a methodological assessment can be weighed for their contribution to the "evidence" that the application of anticholinergic drugs is indeed effective in the treatment of drooling. For the methodological quality of the selected RCT's the internal validity (Table 2.4) was regarded as the most critical aspect.
The RCT by Camp-Bruno[14] acquired sufficient points on internal validity even though the item 'the intention to treat' was graded as insufficient, but the methodological

assessment scores of [3] for randomization (V1) and homogeneity (V2a) compensated for the this. The other RCT's[11;17] did not satisfy the criteria for internal validity. Mier et al did not describe randomization and inclusion criteria and consequently scored moderate on internal validity. In conclusion 1 RCT can be weighed as a "high grade evidence"[14] study, 1 as "moderate grade evidence"[11], and 1 as a "low grade evidence" study[17]. In relation to the objective of this study the RCT by Camp-Bruno contributes most to the evidence. The experimental study with the Virchow design[30] scored 12 out of 12 possible points on internal validity. Although not a RCT this study was judged to provide additional information to the primary evidence.
The cohort study by Reddihough[18] was considered to be a "moderate informative" study. The other two cohort studies by Blasco and Stern[13;20] were regarded as "less informative".

Discussion
For many clinicians the application of anticholinergic drugs is regarded as a realistic possibility to treat drooling and is the first choice therapy. This systematic review investigated the literature for evidence of the effectiveness of anticholinergic drugs in the treatment of drooling in children with multiple handicaps. An overall problem in the studies found is that no single method of measurement of salivary flow and outcome presentation is available. We endorse the plea for the development of a 'golden standard'[1]. Another problem is that in the selected studies that no drug has been repeatedly evaluated. As an outcome of our study no statement can be made about the long-term effects of anticholinergic drug therapy because non of the studies describe a follow-up period greater than a few weeks. Adverse effects were reported in all studies. Only one study provided precise information to what extend side effects necessitate to end the therapy[11]. Frequently reported side effects comprise: irritability, restlessness and over-activity, disorientation, marked pupil dilatation, and constipation. Other, less frequently reported side effects are insomnia, headaches, epileptic seizures, vomiting, difficulty in initiating micturation, dry mouth and lips, 'picking and grasping' movements, and epistaxis.
From the articles by Camp-Bruno and Owen, one can conclude that a daily dosage of 3 mg to approximately 3.8 mg Benztropine should be effective in the treatment of drooling. This implies that Benztropine could be used in the treatment of drooling, although, adverse effects should be thoroughly controlled and no indication of long-term effects can be given. Reddihough provided additional information to support the

evidence of the effectiveness of anticholinergic drugs. A significant reduction in the mean score for drooling was found with a dosage Benzhexol Hydrochloride varying from 2x2mg up to 2x3 mg daily. Mier et al provided support for the primary evidence of the efficacy of anticholinergic drugs. They conclude a marked reduction of drooling in cases Glycopyrrolate was tolerated.

Conclusion

The objective of this study was to investigate the efficacy of anticholinergic drugs to treat drooling in children with multiple handicaps. We performed an in-depth systematic review of the medical literature in order to do a meta-analysis. Unfortunately only seven studies could be identified. Due to the methodological drawbacks within the studies, no general conclusion can be made about the efficacy or average effect of anticholinergic drugs to treat drooling in children with multiple handicaps. Future uniformity in measurements can help the interpretation of outcomes. Further research in larger populations with a longer follow-up period should be encouraged. Based on our study there is some evidence that at least 3 anticholinergic drugs (Benztropine, glycopyrrolate, and Benzhexol hydrochloride) are effective in the treatment of drooling but it cannot be concluded that one anticholinergic drug is preferable above the other. Because of the small number of reports and the methodological restriction within the studies, no meta-analysis could be performed.

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Chapter 3

Salivation in healthy school children

Int J of Ped Otorhinolaryngology 2004; 68/6: 767-774

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Abstract

Objective: To obtain reference data on the unstimulated salivary flow rate in healthy 6 - 11-year-old boys and girls, for use in the treatment of drooling in mentally and physically handicapped children.

Methods: Under standard conditions unstimulated saliva was collected from 62 healthy children using the swab method. Flow rate was determined by calculating the increase in weight of cotton rolls placed in the mouth for 5 min. The influence of the variables age, gender and type of gland were evaluated.

Results: No significant difference was found between the flow rate in boys and girls or among the children in this age window. The swab method showed good reproducibility. The right and left parotid glands had equal flow rates of 0.15 mL/min. The flow rate in the floor of the mouth secreted by the submandibular and sublingual glands was 0.32 mL/min. Conclusions: age and gender did not influence salivary flow rate and therefore needed not to be taken in consideration when measuring salivary flow rate in healthy children 6-11 years of age. The swab method appeared to be reliable, easy to carry out and well-tolerated by the group of school children that was studied.

Introduction

Accurate measurements of salivary flow rate (sialometry) are required in clinical and experimental protocols, for example to monitor the treatment of drooling. In people with neurological dysfunction drooling primarily appears to result from inadequate swallowing and lip-closure due to dysfunctional oral motor activity, and rarely from the excessive secretion of saliva[1].

Parotid gland secretion rates can be measured by intra-oral cannulation of Stenson's duct or by using a Lashley cup or Schneyer's device[2,3]. Measurements of the other major and minor salivary gland flow rates are not performed routinely because of their relative inaccessibility, although some devices have been described[4-7]. Techniques for measuring whole saliva are usually based on draining into a receptable (draining method), collection by aspiration (spitting method) or measuring the increase in weight of an absorbent material that is chewed or placed in the mouth (swab method)[8]. The latter method also enables evaluation of the functional status of the individual glands when the cotton rolls are placed at the glands' orifices.

Salivary flow rates can be measured under unstimulated or stimulated conditions. A range of stimuli can influence salivary flow; gustatory and masticatory stimuli are used most commonly. Unstimulated salivary flow is the flow that occurs in the absence of

any obvious stimulation. The swab method has proved to be a highly reproducible, non-invasive and convenient method, even for the measurement of gustatory stimulated flow rates[9].

It is important to be aware of the many factors that can influence salivary flow rate, in order to keep the sampling procedure as standardized as possible. Variables that may influence flow rate are medication, circadian rhythms[10], prestimulation[11], gender[12-15], age[10,12-15], gland size[16,17], psychological effects[18], and health[30].

Measuring salivary flow rates in young children or physically or mentally handicapped persons is a challenge. Little has been published about the applicability of the different methods to these groups. Unstimulated whole saliva flow rates measured with the draining or spitting method are thought to be unreliable in children of younger than 10 years of age, as these methods depend on the full co-operation of the child who has to sit still for quite some time[14,20]. No research has been done into unstimulated flow rates with the swab method in children.

Measuring flow rates in physically or mentally handicapped children is usually performed to quantify the drool volume. Non-invasive methods involve weighing drooled saliva collected either on a bib or in a plastic bag attached to the subject's chin[21]. Evaporation of saliva over the collection period is not taken into consideration and it can be difficult to achieve effective adherence of tape to a damp chin. Another method is to count the number of bibs or changes of clothing a subject undergoes during a given period of time. However, the decision and timing of when to change a bib or clothing is difficult to standardise. Sochaniwkyj developed an individually-adjusted collection device that is held against the subject's chin by elastic straps attached to an orthodontic head bonnet. This system is unable to collect highly viscous saliva or saliva that does not fall from the lips into the collection system; consequently, such secretions will not be measured[22]. Apart from direct contact methods using devices, an observation method was proposed by Rapp to evaluate leaked saliva. He described the 'Drooling Quotient' to obtain quantitative measures of the percentage of drooling in time-sampling observations[23].

To our knowledge, the swab method has not been used in the evaluation of drooling in mentally and physically handicapped children. We performed a study to evaluate salivary flow rate in healthy primary schoolchildren using the swab method. The aim of the study was to obtain reliable reference data on normal salivary flow rate in boys and girls ranging in age from 6 to 11 years, for use in the treatment of drooling. The influences of age and gender on salivary flow rates were investigated.

Materials and methods

Subjects

Sixty-two healthy children were recruited from two primary schools. The population comprised 34 boys and 28 girls, ranging in age from six to 11 years. Levene's test for Equality of Variances showed equal distribution of age (t=-0.67; df=60;*p*=0.51) in the boys (mean age 8.03 years, SD 1.83) and the girls (mean age 8.32 years, SD 1.54). Subjects taking medication that would influence the quantity and quality of the salivary secretion were excluded. None of the children reported complaints suggestive of salivary gland dysfunction or displayed evidence of intra-oral soft tissue disease. The parents gave informed consent.

Salivary Collection Method

Saliva was collected under standardized conditions according to the method described by Poth[24]. Three dental cotton rolls, of exact known weight, were placed in the mouth that had previously been dried with sterile gauze. One roll was placed under the tongue at the orifices of the ducts of the sublingual and submandibular gland, while the other two rolls were placed in the upper vestibules at the opening of each parotid gland duct. The children were asked not to chew on the cotton rolls. At the end of a 5- minute collection period, the cotton rolls were removed and immediately weighed. A duplicate of the test was performed after a 15-minute interval. Unstimulated salivary flow rates were calculated in mL/min for the right parotid, left parotid and submandibular plus sublingual glands. As the Specific Gravity of saliva is 1.0 volume and weight were used interchangeably.

The cotton roll placed in the floor of the mouth absorbed the secretion of the two submandibular and sublingual glands. The sublingual glands are known to contribute about 5% of the saliva. Using this method, sublingual and submandibular salivas were collected together and are referred to as the submandibular flow rate. To control for diurnal and inter-examiner variation, all samples were collected in the morning by the same examiner, after a 1 h fast from food or drinks.

Statistical Analysis

Between-variable correlations were tested: flow rate versus age, flow rate versus gender, right parotid versus left parotid flow rate, parotid versus submandibular flow rate. Test-retest reliability was calculated. Statistical analyses were performed using (One-way) ANOVA's or paired t-tests.

Results

All the children could easily perform the test and no one had to be withdrawn from the study. For technical reasons, only one measurement was performed in two of the 6 year-olds.

Addition of the left parotid, right parotid and submandibular flow rates resulted in the whole saliva flow rate. The flow rates of unstimulated saliva per age group for each gland are shown in Table 3.1.

Table 3.1: Mean unstimulated salivary flow rate (ml/min) per age group

Gland	Age in years (number of subjects)					
	6 (n=10)	7 (n=14)	8 (n=10)	9 (n=10)	10 (n=10)	11 (n=6)
SM	0.32	0.34	0.30	0.31	0.36	0.30
Par R	0.22	0.14	0.14	0.12	0.20	0.12
Par L	0.25	0.13	0.13	0.12	0.18	0.12
Whole	0.78	0.60	0.57	0.55	0.74	0.54

SM= submandibular (i.e. flow rate of right and left submandibular and sublingual glands),
Par R= right parotid, Par L= left parotid, Whole= whole saliva

Gender

The mean whole saliva flow rate obtained during the first measurement, rated 0.69 mL/min (range 0.22-1.26 mL/min; SD = 0.32) for the boys (N = 33) and 0.54 mL/min (range 0.14- 1.30 mL/min; SD = 0.30)for the girls (N = 28). No significant differences excited between the flow rates of boys and girls during the first measurement (One-way ANOVA: F = 3.12; df = 1,59; p = 0.08), This was confirmed in the whole saliva flow rates during the second measurement (F = 0.64; df = 1,59; p = 0.43).

Age

Comparison of the mean unstimulated whole saliva flow rates between age groups did not reveal any significant differences (ANOVA: first measurement F = 0.29; df = 1,59; p = 0.60, second measurement F = 1.83; df = 1,59; p = 0.18). In addition, there were no age-related differences between the flow rates of the right parotid (F = 1.21; df = 6,53; p = 0.32) and left parotid gland (F = 2.03; df = 6,53; p = 0.08). Further analysis of the different age groups according to the Duncann procedure (post hoc test), again, did not reveal any significant differences.

Test-Retest reliability

The mean values of the whole salivary flow rates obtained during the first and second measurements were not significantly different. Test-retest reliabilities after comparing the results of the two collection samples were, however, significant for all three glands (Table 3.2).

Right versus left parotid values

There appeared to be no significant difference in mean flow rate between the right and the left parotid glands (paired samples test: t = -0.117; df = 60; p = 0.91, correlation 0.84).

Table 3.2: Test-Retest reliability

Gland	1st measurement (ml/min) ± SD	2nd measurement (ml/min) ± SD	Correlation	Significance
SM	0.31 ± 0.12	0.33 ± 0.11	0.72	t=-1.5; df=59; p=0.15
Par R	0.15 ± 0.13	0.16 ± 0.12	0.75	t=-1.023; df=59; p=0.31
Par L	0.16 ±0.11	0.15 ± 0.13	0.81	t=0.38; df=59; p=0.70
Whole	0.62 ± 0.32	0.65 ± 0.31	0.83	t=-1.14; df=59; p=0.26

Correlation between the first and second measurement, Significance of the difference between the two measurements calculated with a paired t-test.
SM= submandibular (i.e. flow rate of right and left submandibular and sublingual glands), Par R= right parotid, Par L= left parotid, Whole= whole saliva.

Parotid versus submandibular flow rate

There was a high correlation (first measurement: 0.54, second measurement: 0.66) between the combined flow rates of the right and left parotid gland (0.31 mL/min; SD = 0.24) and the submandibular flow rate (0.31 mL/min; SD = 0.12). Subjects with a higher parotid flow rate also demonstrated a higher submandibular flow rate.

Discussion

The level of unstimulated parotid, submandibular and whole saliva flow rates were independent of gender or age. These results are in accordance with those of Andersson whose unstimulated whole saliva was of the same order in boys and girls of 10 years old, whereas 13-year-old boys had higher flow rates than girls[14]. Shannon & Feller did not find any significant differences in unstimulated parotid flow rates between boys and

girls ranging from 3 to 16 years[12]. In contrast, Lopez established a sex-related difference in unstimulated whole saliva flow rate: males, aged 5 - 77 years, had higher flow rates than females of the same age. Comparison with the present study is impossible, because of the extremely wide age distribution of the participating persons[25]. It has been suggested that the lower flow rates in females can be explained by to the smaller size of their salivary glands[15]. However, no representative material for comparison with respect to the salivary gland size in children is available in the literature. Our results showed that in the treatment of drooling until puberty, no gender effect has to be taken into consideration.

In this study, no age-related decline or increase was noted in the unstimulated salivary flow of boys and girls between 6 to 11 years of age, although a relatively high flow rate was found in the 10-year-olds (Table 3.1). It is unclear why a larger number of the 10 year-olds had whole saliva flow rates of more than 1 mL/min compared to the other age groups. Reviewing the test diary revealed that one of these children had lost a molar 1 day prior to the measurement, one was suffering from a clinically non-relevant common cold, and two children were shedding their teeth; the latter was a common feature in all the age groups.

Andersson measured equal unstimulated whole saliva flow rate in 10 and 12-year-olds and Kavanagh in 12 and 13-year-old children[13,14]. Andersson compared the flow rates of children to those of adults using the spitting method. In agreement with Lourie (1943) he suggested general high salivary activity in children of school age that decreased with increasing age due to maturation of the autonomic nervous system. However, Becks and Shannon & Feller found that unstimulated parotid flow rate increased significantly with increasing age in children ranging from 3 to 16 years[12]. This is in contrast with our findings. No other reports have been published on the unstimulated salivary flow rate in children of comparable age to those in the present study. According to our results age is not an important factor when measuring salivary flow rate up to the age of puberty.

The swab method applied in this study to determine salivary flow rate showed good reproducibility and reliability, independent of age or gender in boys and girls aged from 6 years and onwards. All the individuals were able to complete the procedure. In some cases the collection period had to be limited to 4 min, because the cotton rolls were no longer tolerated. Three children reported transient cramp in their cheek.

In conclusion, the swab method was reproducible, easy to carry out and well-tolerated, even in a group of well-instructed 6-year-old children. In the case of a small oral cavity, we recommend to reduce the size of the cotton rolls.

Reproducibility was not effected by age, gender or the type of salivary gland. Although it was easier to position the two cotton rolls in the buccal cavity than the one sublingual, and the former seemed to stay in place better during the 5-minute collection period, the flow rates at the different sites were equally reproducible.

Subjects with a higher parotid flow rate also had a higher submandibular flow rate. An increase in parotid flow rate caused by chewing on the cotton rolls can be ignored as a source of methodological error, because chewing does not stimulate the submandibular glands.

Other authors found higher flow rate values during the second testing session[11,14,15]. They believed that the children were more familiar with the procedure, which led to better co-operation and diminished negative influence of stress on the secretion rate. In this study, although we found some variation between the first and second testing sessions, there were no significant differences. This is in accordance with the study by Crossner[10].

The unstimulated whole saliva flow rates obtained using the present set-up were somewhat higher than those measured with various methods that have been published over the past 50 years (Table 3.3). Differences between the present values and those reported by others can be explained by the dissimilarity in subjects, collection conditions and devices. Comparing the research using the swab method, only Lopez' study comprises, besides adults, children of the same age as the present study does. The low values found in that study may have been due to the participation of seniors and the fact that the subjects kept their eyes closed during sampling to avoid the influence of visual stimuli.

Table 3.3: Unstimulated whole salivary flow rate

Author	Method	N	Age	Gender	Flow rate (mL/min)
Becks (1939)	ND	40	9-48	M+F	0.22-0.66
Becks & Wainwright (1943)	ND	661	5-95	M+F	0.25-0.40
Peck (1958)	swab	16	adults	M F	1.42 1.29
Andersson (1972)	spitting	296	10 13	47 M / 53 F 47 M / 49 F	0.39 / 0.38 0.46 / 0.33
Dawes (1973)	draining	7	adults	M+F	0.46
Gutman (1974)	spitting	22	6-76	M+F	0.09-0.96
Navazesh & Christensen (1982)	draining spitting suction swab	17	18-32	M+F	0.47 0.47 0.54 0.52
Heintze et al. (1984)	draining	629	15-74	M / F	0.36 / 0.26
Ben-Aryeh et al. (1984)	spitting	31 30	26 69	M + F M + F	0.47 0.29
Percival et al. (1994)	spitting	116	20-80	M / F	0.50 / 0.33
Watanabe et al. (1995)	draining	30	5	M + F	0.26
Lopez (1996)	draining swab	159	5-77	M + F	0.23 0.31
Kavanagh et al. (1998)	draining	43	12-13	M + F	0.46-0.82
Present study	swab	60	6-11	M + F	0.46

M= male, F= female, ND= not described

Our unstimulated parotid flow rates were higher than those reported in the literature (Table 3.4). Shannon & Feller were the only authors who measured unstimulated parotid flow rate in children using a collection cup; they found flow rates of 0.03-0.04 mL/min[12]. Perhaps the swab method used in our study stimulated the parotid glands through oral tactile stimuli by the examiner or chewing on the cotton rolls by the subject, although manipulation of the oral musculature was prevented as much as possible and the subjects were instructed not to chew on the foreign object placed in their mouth.

Table 3.4: Unstimulated parotid flow rate

Author	Method	N	Age	Flow rate (ml/min)
Shannon (1967)	ND	4589	17-22	0.04
Dawes & Chebib (1972)	Lashley cup	31	young adults	0.05-0.07
Dawes (1973)	Lashley cup	7	adults	0.07
Dawes (1975)	ND	9	adults	0.04-0.06
Shannon & Feller (1979)	Cup	33 54 64 56	3- 6 7 - 8 9 - 10 11-16	0.03 0.03 0.04 0.04
Heft & Baum (1984)	Carlson- Crittenden cup	85	23-81	0.04-0.06
Moret et al. (1993)	Curby collection device	30	19-25	0.10
Present study	Swab method	60	6-11	0.15

ND= not described

When we compared our results to the stimulated parotid flow rate described in the literature, our finding of 0.15 mL/min was much lower (Table 3.5). Thus it can be concluded that the swab method causes little or no stimulation. With higher parotid flow rates, the proportional contribution of the parotid glands to whole saliva volumes increases. In this study the parotids accounted for 50% of the unstimulated whole saliva, whereas others mentioned 21% to 26%[26,27]. Malpani used a non-invasive scintigraphic method to quantify unstimulated secretions from individual salivary glands and found the fractional output rate of the submandibular glands to be three times higher than that of the parotid glands[28]. Thus our results imply that the parotid glands made a relatively higher contribution to the whole saliva. An explanation for this dissimilarity might be the presence of remnant saliva in the floor of the mouth after removal of the cotton swab.

Table 3.5: Stimulated parotid flow rate

Author	Method	N	Age	Flow rate (ml/min)
Ferguson et al. (1973)	Lashley cup	27	adults	1.22
Shannon et al. (1974)	ND	368	17-22	1.01
Dawes et al. (1978)	ND	30	19-39	0.25-0.98
Ahlner & Lind (1983)	swab method	150	15-80	Par R: 1.28 Par L: 1.32
Baum (1981)	Carlson- Crittenden cup	208	23-88	0.71-0.96
Heft & Baum (1984)	Carlson- Crittenden cup	85	23-81	0.62-0.84
Nederfors & Dahlof (1993)	Carlson- Crittenden cup	29	29-43	1.50
Percival et al (1994)	Lashley cup	116	20-80	0.59 (M)/ 0.45 (F)

M= male, F= female, Par R= right parotid gland, Par L= left parotid gland

Copious secretions can overflow the swabs. Measured secretions would then be underestimated, because of saliva losses. This was observed in only four children. To avoid overflow in patients examined on the suspicion of hypersalivation, the collection period can be reduced. Still, our finding of 0.32 mL/min for both the submandibular glands (and sublingual glands) is similar to those reported in other research in which the flow rates of both, or only one submandibular gland are measured in adults (Table 3.6). The subjects investigated by Sheebny, Enfors and Malpani were adults[26-28]. In children, the parotid glands in the unstimulated condition may be more highly active than in adults.

Measuring salivary flow rate with a Lashley cup is a very precise method that can easily be carried out by a co-operative patient. Unfortunately, it is of no practical use for young children, or especially for the mentally and physically handicapped. In conclusion, the swab method proved to be reliable, well-tolerated by young children and suitable for use in a clinical setting. However, possible oral stimulation must be taken into consideration, which might impede comparison with results obtained with other methods. This study showed that the variables age and gender do not influence the salivary flow rate in a group of healthy 6 to 11-year-old children.

Table 3.6: Unstimulated submandibular / sublingual flow rate

Author	Method	N	age	Flow rate (ml/min)
Schneyer (1955)	device which separately collects SM (right + left) and SL saliva	ND	young adults	0.15 M
Enfors (1962)	Device	54	20-59	0.10
Dawes (1975)	Device	9	young adults	0.16
Pedersen et al. (1985)	device using suction with micropipette	58	18-35 >66	0.07 M/ 0.05 F 0.01
Coudert et al. (1986)	device with two collection cups and vacuum system	34	adults	0.16
Tylenda et al. (1988)	device using suction with micropipette	90	26-39 40-59 >60	0.15 M/ 0.21 F 0.23 M/ 0.12 F 0.13 M/ 0.15 F
Oliveby et al. (1989)	silicone device	5	26-38	0.11
Atkinson et al. (1990)	Device	298	22-72	0.11 F
Ship et al. (1991)	Device	102	20-90	0.11 M/ 0.10 F
Moret (1993)	Coudert's device	30	19-25	0.25
Wolff et al. (1997)	device using suction with vacuum pump	10	25-81	0.17
Truelove et al. (1967)	Device	25	5-32	ND
Ferguson (1974)	Truelove's device	15	adults	0.26
Present study	swab method	60	6-11	0.32

Research under market line measured flow rate of both submandibular glands. Above the market line only one gland is measured.
M= male, F= female, ND= not described, SM= submandibular gland, SL= sublingual gland

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Chapter 4

Assessment of salivary flow rate: biological variation and measure error

Laryngoscope (2004): in press

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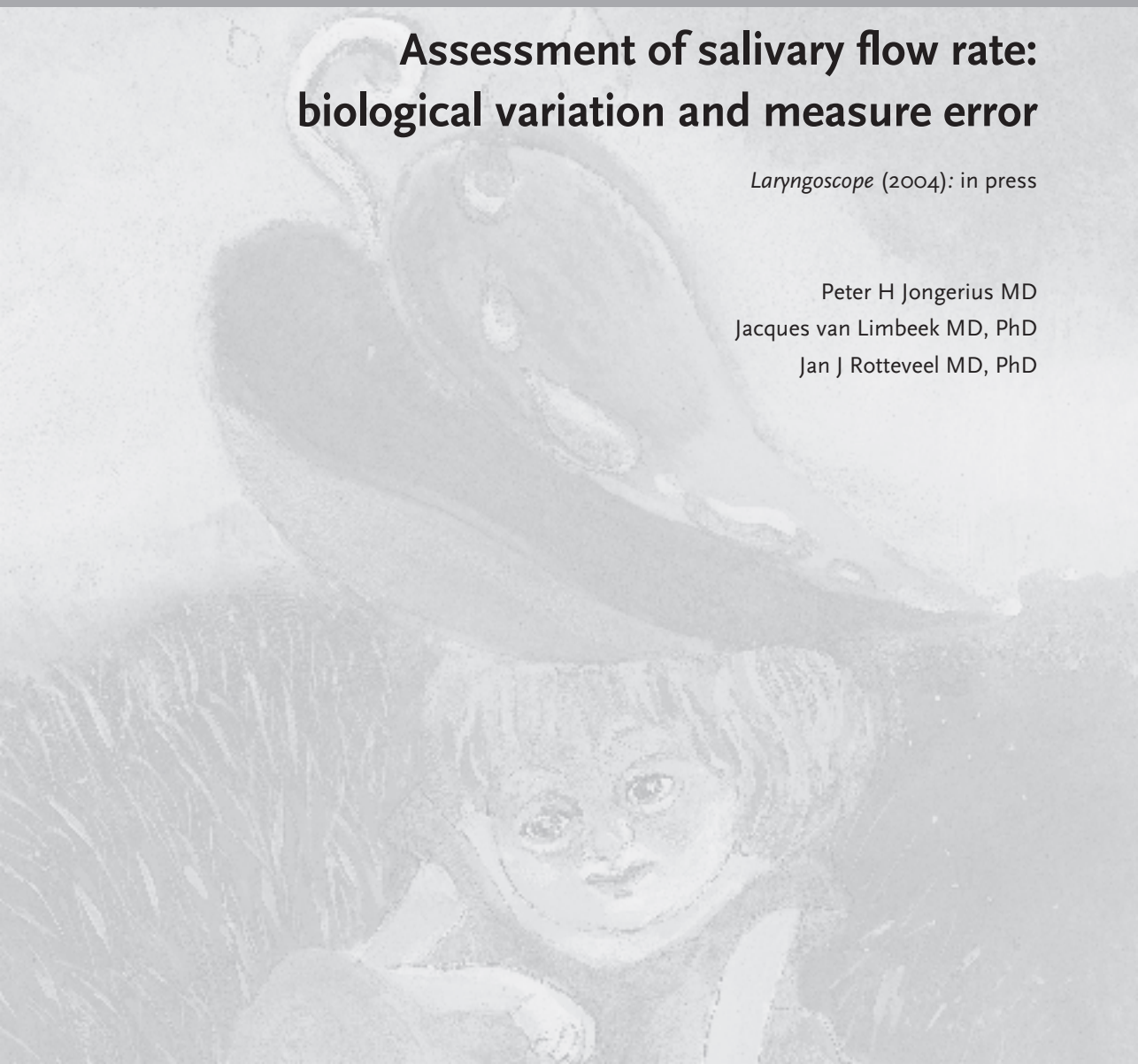


Abstract

Objective: to investigate the applicability of the swab method in the measurement of salivary flow rate in multiple handicapped drooling children; to quantify the measurement error of the procedure and the biological variation in the population. *Study design:* cohort study. Methods: in a repeated measurements design, baseline series of salivary flow rates were obtained from 45 children. The within-subject standard deviation (SW) was calculated to express the measurements error according to a procedure introduced by Bland and Altman. Results: 224 samples (mean=0.40 ml/min., SD=0.19 ml/min.) were obtained and analyzed. The results of this study indicate that consistent scores were obtained at subsequent measurements and good parity existed between the two measurements of salivary flow rate at each session. The SW could be estimated (0.11 mL/min), which was applied to quantify the specific variation of the salivary flow rate in our population. Conclusion: according to Bland and Altman, the within-subjects standard deviation (SW), being a quantification of the measurement error and biological variation, was found to be a useful tool to evaluate the obtained baseline salivary-flow rate measurements. The swab method can well be used to evaluate salivary flow rates in drooling children with cerebral palsy, during interventional studies that aim to reduce the saliva production.

Introduction

Drooling in multiple handicapped children is predominately caused by a disturbance in oral motor control[1]. It is generally accepted that handicapped children do not produce a greater amount of saliva compared to healthy subjects. The evaluation of drooling is difficult, because saliva secretion varies from moment to moment within a subject. Besides, the level of salivary flow at which a person demonstrates drooling, may differ among patients.

Rating scales are used to investigate the severity and frequency of drooling. The Teacher drooling scale (TDS), the drooling severity scale, and the drooling frequency scale are examples (Table 4.1)[2;3]. Visual analogue scales (VAS), which investigate the parents' opinion, are also applied[4]. The Drooling Quotient (DQ) is a semi-quantitative observational method (expressed as a percentage) comprising two 15-minute periods of observation separated by a 30-minute break[5;6]. In terms of objectivity, the cannulation of the salivary ducts is referred to as the 'gold standard'[7].

Table 4.1: Drooling Rating Scales

Scale	Teacher Drooling scale[#]	Drooling Severity Scale	Drooling Frequency scale
1	No Drooling	Never drools Dry	Never drools
2	Infrequent drooling Small amount	Mild Only lips wet	Occasionally drools
3	Occasional drooling Intermittent all day	Moderate Wet on lips and chin	Frequently drools
4	Frequent drooling But not profuse	Severe Clothing becomes wet	Constantly drools
5	Constant drooling Always wet	Profuse Clothing, hands, tray and objects become wet	

[#]Thomas-Stonell N, Greenberg J. *Dysphagia:* 1988.

During this direct investigation technique, parotid secretion is collected by using special devices that cover the orifices of Stenson's ducts. These procedures have serious practical limitations in non-cooperative subjects. Direct flow rate measurements from other major and minor salivary glands are not routinely performed because of their relative inaccessibility. Weighing of bibs in which spilled saliva has been collected, is also described[8]. The application of functional salivary gland imaging, using technetium scanning, has been suggested[7]. The exposure of young patients to radiation has to be carefully weighed and is probably contra-indicated for a non-life threatening condition like drooling.

In sialometry dental cotton rolls can be used, placed at the orifices of the ducts of the salivary glands[9]. The outcome of this swab method is the increase in weight of the absorbent material in a fixed time interval, transformed to either g/min. or mL/min. The swab method has proved to be a highly reproducible, non-invasive and convenient method even to measure gustatory stimulated flow rates[10]. The swab method can be applied to evaluate the salivary flow in a population under varying conditions (e.g. stimulated versus unstimulated saliva production). So far the observations were mainly conducted in healthy adult subjects[11].

The magnitude of the measurement error, introduced during the swab method, is influenced by the biological variation of saliva production within the subject and between subjects. In addition, the measurement procedure itself will cause variation despite its standardization for example by creating an oral stimulus when inserting the

dental rolls. Measuring salivary flow rates in physically or mentally disabled children remains a challenge. In particular, this is true for a group of drooling children.
In principle, the results of therapies that aim to reduce the salivary flow (anticholinergic drugs and Botulinum toxin) can be evaluated by the swab method. However, application of the procedure has its limitations. In the event surgery is executed, such as the rerouting of Wharton's duct, the swab method is useless because after the operation there is no orifice left to place the cotton roll.
To our knowledge there are no decisive data about the applicability of the swab method for multiple disabled children. In recent literature some preliminary reports have been published on this subject[7;12]. The objective of this article is to present data of repeated salivary flow measurements from the submandibular glands, using the swab method, in a population of drooling children with cerebral palsy (CP). The measurement error and biological variation in the population will be quantified by the within-subjects standard deviation (SW), according to the method designed by Bland and Altman. Clinicians would be able to use this specific information to evaluate the results of interventions undertaken to treat drooling in a group of handicapped children.

Patients and method

Patients

A score of 3 or higher on the TDS (Table 4.1) was demanded for children to be enrolled in the study.
Forty-five children were included; 28 male; 17 female; age 3-16 years (mean 9.5, SD 3.7). All entered a qualification period in which inclusion and exclusion criteria were assessed (Table 1.3).
Eight were ambulant without aid; 37 had wheelchairs; 22 could not talk; 29 attended a special education school; 14 went to a daycare center for mentally handicapped children.
Repeated measurements of salivary flow are reported in this study.

Procedures

For all children, salivary flow measurement sessions were scheduled with an interval of several days. At each session, 2 repeated measurements of salivary flow rate, separated by a 30-minute interval were carried out. In this manner, 3 or 4 pairs of repeated measurements were obtained from each child. Patients were evaluated in the morning, at least one hour after a meal, while they were awake and were positioned

erect. Prior to the assessment the mouth was cleaned and dried by gauze. Using the swab method, dental cotton rolls (Salivette®, Sarstedt BV, Etten-Leur, The Netherlands) were positioned at the orifices of the ducts of all major salivary glands, in order to collect saliva from the left parotid and right parotid (Stenson's duct), the submandibular glands (Wharton's duct), and the sublingual glands. The dental rolls were placed in a fixed order as quick as possible, starting in the upper region of the mouth. The endings of the Stenson ducts were covered to prevent saliva from leaking into lower parts of the oral cavity. In this way saliva was obtained separately from the different oral regions. The submandibular and sublingual ducts have a close anatomical relation so that separate measurements could not be obtained. The compound measurement of these glands is simply referred to as submandibular salivary flow (SubFl). During a 3 to 5-minute period, the cotton rolls absorbed sufficient saliva so that an increase in weight could be measured and the rolls were not over-saturated. The rolls were weighed before and after the procedure using an electronic device that was sensitive to 0.01 gram.

We scored the physical condition of each patient at all measurement moments in relation to flu, and oral or airway pathology. These conditions can influence saliva production and are regarded as 'confounders'. The remarks made by the speech therapist were checked with respect to the child's condition. Based on these findings some data were marked as 'outliers'. These data (explained outliers) were eliminated from the database.

Analysis

Analysis of data was restricted to the submandibular flow rates. It is generally accepted that the submandibular glands produce 60 - 70% of the secreted saliva at rest, meaning that one does neither eat nor drink.

If parity existed between subsequent measurements using the swab method, the difference between these two measurements is expected to be approximately zero irrespective of the magnitude of the measurements. A rank correlation (Kendall's tau) was calculated to assure that the spread of the differences of pairs of observation could be regarded as a non-systematic (random) process. To use the procedure as suggested by Bland and Altman, it was required that the variation of differences was independent of the magnitude of the mean. To visualize this, scatter diagrams were plotted of the absolute values of the difference against the mean of these scores. In this way, it was determined whether or not only random error was found in the data.

As mentioned above, the differences of pairs of observations in one patient should be zero. This is also true for the mean differences of the group. If the mean difference (all patients of a certain measurement moment) is significantly different from zero, we would not be able to use the data. We therefore calculated the mean within-subject difference for all patients at each session.
The method, described by Bland and Altman, to quantify the measurement error by the use of a repeated measures design was applied[13;14].
Central in this concept is the within-subject standard deviation (SW) calculated as:

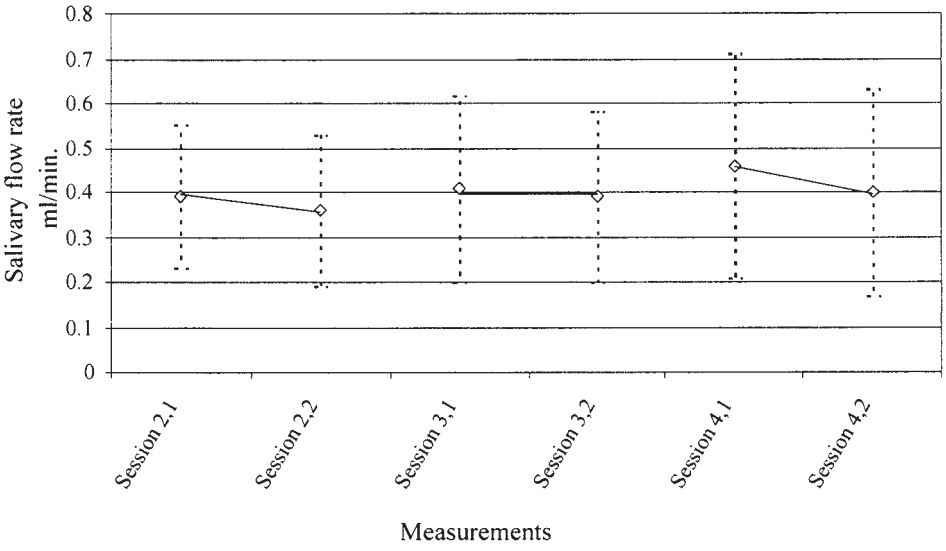
$$SW: \sqrt{\sum_{i=1}^{i=N} \frac{(d^2)}{N}}$$

In this formula d^2 (the square of the standard deviations) actually represents the variance of the scores and d^2/N is in fact the mean within-subject variance[15]. The mean within-subjects variance can be calculated using a one-way ANOVA (available in various computer programs) to determine the 'residual mean square'. The SW, in turn, is calculated by taking the square root.

Results

Of all observations, 22 were identified as explained outliers[13]. Thirteen of these 22 outliers were taken during the first session and were produced by 22% of the patients. Considering the remarks made by the speech therapist, the first session seemed to be influenced by factors as anxiety and uncontrollable intra-oral sensory stimuli resulting in refusal to allow the dental rolls to be placed. The first session most likely should be regarded as a learning curve. Patients refusing the dental rolls during the first session did cooperate fully in the following sessions. Therefore, the data of the 2nd, 3rd and 4th sessions are regarded as the most representative data and were used for further analysis.
The means and standard deviation of SubFl at the separate session are shown in Fig. 4.1 and tabulated in Table 4.2. It was concluded that the calculated means of the salivary flow rates were in the same range during the entire study.

Figure 4.1: Mean submandibular flow at each measurement



The remaining 9 of the 22 outliers, produced by 5 children, were randomly spread. On one occasion the parents of the child reported fatigue because of exhausting school activities the same morning, one child had an epileptic seizure the day before the assessment, one child had a cold, one child liked to chew on the dental rolls possibly influencing the outcome, and the last child liked to chew on the rolls but also had a cold. These conditions were assumed to explain the deviation in sufficient detail.

Table 4.2: Mean submandibular flow at each measurement

Session*	2;1	2;2	3;1	3;2	4;1	4;2	Overall
Mean	.39	.36	.41	.39	.46	.40	.40
SD	.16	.17	.21	.19	.25	.23	.19

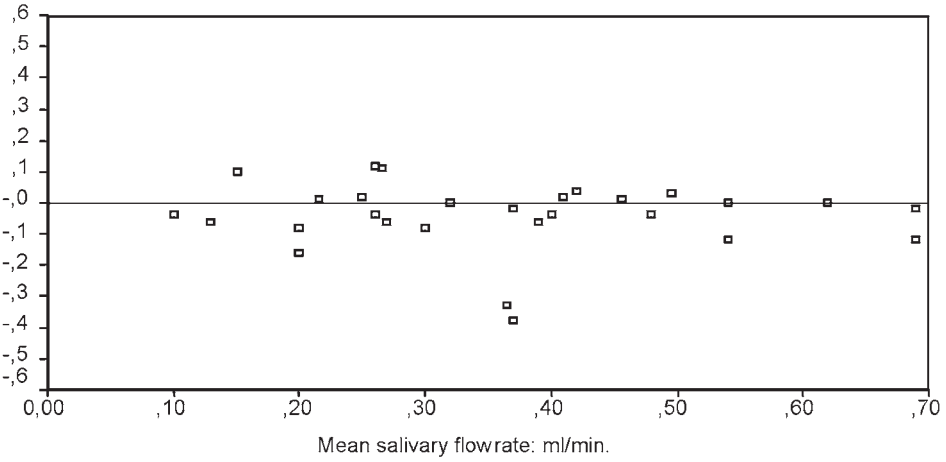
*Number indicating session and measurement

After discounting the first session and eliminating the outliers mentioned above, 224 samples remained for further analysis (mean=0.40 ml/min., SD=0.19 ml/min, table 4.2).

To determine SW the first step of the Bland and Altman procedure was taken. Off all pairs of salivary flow measurements, the within-subject differences between the two

measurements at each session were calculated and graphically depicted. Figure 4.2 is the scatter diagram of the second session with the separate within-subject differences of each patient plotted against the mean of the two scores[13-15].

Figure 4.2: Within-subject differences against the mean (2nd measurement session)



Values below zero occurred in cases the second measurement was higher than the first. With the exception of two cases, most differences were clustered around zero. The estimated rank correlation showed no significant relation between the magnitude of the mean and the differences of the SubFl values (Kendall's tau 0.41; non-significant). From this, it was concluded that the spread of the differences of pairs of observation could be regarded as a non-systematic (random) process.

In addition, the mean difference for each of the four sessions was calculated (range 0.01 to 0.05 mL/min). The result supported the fact that the differences of repeated SubFl measurements of all patients at one particular session approximated zero. The above-mentioned steps were needed to allow calculation of the within-subjects standard deviation.

Using a computer aided ANOVA, the SW for the sessions "2 through 4" was calculated (SW[2-4] = 0.11 mL/min).

Discussion

The objective of this study was to investigate the clinical applicability of the swab method in a population of multiple handicapped children. This was executed by quantifying the measurements error and biological variation of the salivary flow rate

by means of the within-subjects standard deviation (SW) in a repeated measurements design. Salivary flow rates were obtained from the submandibular glands by the swab method. Utilizing the absorbent properties of dental rolls, 224 samples were collected. The outcome of the swab method was the increase in roll weight (mL/min.) before and after the collection of saliva from individual oral regions. The results of this study indicate that consistent scores were obtained at subsequent measurements.

Taken the population into account, it was expected to meet considerable variation with-in and between subjects. The degree of the variation in repeated measurements represents biological variation over time, as well as error in the measurement procedure itself. According to Bland and Altman, this variation can be quantified by means of the within-subjects standard deviation (SW), which is expressed as 1 x SW, 2 x SW or $1.96\sqrt{2}$ x SW. The last option equals 2.77xSW and is used to determine the limits of agreement[13]. Calculation of the SW in baseline observations offers a clinically relevant way to delineate the population before treatment. The SW expresses to what extent the parameter (in this case salivary flow rate) will vary in a repeated measurement design, assuming standardized conditions. In addition, it gives the clinician a tool to decide whether an intervention in the treatment of drooling leads to a real improvement; a decrease in salivary flow rate greater than SW. The SW represents an entity based on data of the entire population and should not be applied to an individual subjects. The SW is specific for each population and is to be calculated for every new research program. In particular, interventional studies aiming to reduce the salivary secretion from the salivary glands (e.g. Botulinum toxin, anticholinergic drugs) may benefit from this approach. Regarding the upcoming interest in the Botulinum toxin in the treatment of drooling, it is foreseeable that many research programs on this subject will be undertaken in the next years. In addition, it should be mentioned that salivary flow measurement by the swab method is of limited meaning in some surgical procedures. For example the salivary flow from the submandibular gland cannot be accurately measured after relocation of Wharton's duct.

Drooling in handicapped children is a serious clinical problem. The description of the different treatments to reduce or to redirect the salivary flow rate is beyond the scope of this article. No treatment option available is universally successful. It seems to be an incurable problem and treatment aimed at reducing salivary flow is a good approach in many cases, which can be assessed by the swab method. An experienced speech therapist should carry out the swab method and the child must accept the dental rolls. In general, the first session ought to be regarded as a learning curve.

If the measurements are part of a research program at least two pairs of repeated measurements should be available in order to calculate the SW.

To be conclusive about the result of any intervention the clinician has to decide at what point the treatment can be considered to be effective. For clinical practice the SW indicates a minimal change in the salivary flow rate in order to be sure that the outcome cannot be attributed to sources of error.

In relation to the mean of our population (0.40 mL/min.) a positive change of 1 x SW (0.11 mL/min.) or more, as a result of therapy, would mean a decrease of salivary flow of 25%. We concluded that an improvement of (more than) 1 x SW implicated a notable change in the salivary flow compared to baseline.

In conclusion, the swab method can be applied to measure salivary flow rates in a group of drooling handicapped children. According to Bland and Altman, the within-subjects standard deviation (SW), being the quantification of the error in the measurement procedure and the biological variation, was found to be a useful tool to evaluate the obtained salivary-flow rate measurements.

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Chapter 5

The treatment of drooling by ultra-sound guided intra-glandular injections of Botulinum Toxin-A into the salivary glands

Laryngoscope 2003; 113:107-111

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Abstract

Objective: The aim of this article is to present backgrounds, the procedure, and technique of bilateral ultra-sound guided, single dose injections of Botulinum neurotoxin type-A (BONT) into the salivary glands in patients suffering from severe drooling. *Study design:* Clinical trial.

Methods: Initially, an in-vitro study was performed to determine the volume of the dilution of BONT required for optimal spreading and to gain insight in the spreading pattern of the fluid in the submandibular gland. Subsequently, patients with severe drooling were included in a clinical study. Salivary flow was measured under standardized conditions, and BONT was injected into the submandibular glands with the patient under general anesthesia and with ultrasound guidance as an outpatient procedure or during a short stay at the daycare unit.

Results: BONT for each gland should be diluted in a volume of 1 to 1.5 mL of saline to achieve adequate spreading within the gland and to diminish the risk of diffusion into surrounding structures. With ultrasound guidance, separate structures surrounding the glands and structures within the glandular parenchyma are well recognized and injection errors can be avoided.

Conclusion: With the procedure described, it is possible to accurately inject BONT directly into the glandular parenchyma and to visualize spreading of the fluid in the glandular parenchyma. It is found to be a safe method that guarantees an optimal clinical effect and avoids potentially harmful side effects. We recommend ultra-sound guidance if injections of BONT into the salivary glands are considered.

Introduction

Drooling is an important clinical, social, and emotional issue for people with severe neurological disease such as cerebral palsy in childhood and Parkinson's disease or amyotrophic lateral sclerosis (ALS) in adults[1;2].

Salivation is mediated through the autonomic nervous system in which the salivary glands function under a complex parasympathetic and sympathetic neural control. Parasympathetic nerves provide the main drive for glandular secretion. Sympathetic impulses appear to evoke specialized responses that tend to modulate the composition of the saliva. Nerve endings within the parasympathetic postganglionic system secrete acetylcholine, and blocking these receptor sites inhibits nervous stimulation to the salivary glands. The application of Botulinum toxin type-A (BONT) to treat drooling is still experimental and subject to research. Because of the pharmacological properties

of BONT, it has been postulated that BONT might reduce salivary flow from the salivary glands[3]. BONT is applied to diminish the salivary flow rate, to reach a balance between the quantity of secreted saliva and the swallowing capacity of the particular patient. The main goal of the treatment is to reduce drooling[1]. However, the injection of BONT into the surrounding structures of the salivary glands could lead to unintended clinical effects. For example, deposition of BONT in the muscles can cause paresis with disturbance of deglutition. Before the intra-glandular treatment can be tested, the injection procedure must first be evaluated.

The aims of the present report are to present an in-vitro study and to demonstrate the technique and results of the in-vivo injections into the submandibular glands in children with severe drooling.

The theoretical possible adverse effects of unintended injections into the surrounding structures of the glands are discussed for the submandibular glands as well as for the parotid gland.

Material and method

In vitro study

An in-vitro study was performed in order to determine the anatomical distribution of injected fluid into the submandibular glandular parenchyma and to determine the volume to which dilution was needed to obtain optimal spreading. A normal submandibular gland was obtained from a surgical procedure in which the gland had to be removed as part of a radical neck dissection. Immediately on removal, the parenchyma of the isolated gland was injected. Two injection sites representing a realistic in vivo approach were chosen and injected with an increasing volume up to 1.5 mL Omnipaque (140 mg/mL). Omnipaque was used because it is a water-soluble contrast medium with the same viscosity as a BONT solution. The application enabled X-ray investigation of the gland at several stages of injected volumes.

In vivo study

Children with cerebral palsy and with severe drooling who visit our specialized interdisciplinary outpatient clinic could be included in our clinical trial to treat drooling with BONT. The inclusion criteria (Table 1.3) had to be satisfied: (1) no medical condition contra-indicating therapy with BONT, (2) no prior injection with BOTOX® for any other indications within 6 months before entrance in the study, (3) no known hypersensibility to BOTOX® or any ingredients of the formulations, (4) no use of anticholinergic drugs,

and (5) a score of three or higher on a drooling severity scale and frequency scale severity scale or a score of 3 or higher on the TDS (Table 4.1 and 5.1)[4].
Written informed consent was obtained from the parents or caretakers. The Hospital Ethics in Human Research Committee approved the study.

Table 5.1: Questionnaire-based scoring system for drooling severity and frequency (Thomas-Stonell N, 1988)

Drooling severity	**Drooling frequency**	
1 Dry	Never drools	1 Never drools
2 Mild	Only lips wet	2 Occasionally drools
3 moderate	Wet on lips and chin	3 Frequently drools
4 Severe	Drools to extent the clothing becomes damp	4 Constantly drools.
5 Profuse	Clothing, hands, tray and objects become wet	

Measurements
All subjects were evaluated with repeated salivary flow measures from both the submandibular/sublingual glands and the left- and right-side parotid glands before and at regular intervals up to 24 weeks post BONT injections. Absorbent cotton rolls positioned at the orifices of the salivary ducts were weighed sequentially before and after the procedure of saliva collection[1]. Patients were evaluated while awake and sitting erect. The interval between the investigation and the last meal was at least 1 hour.

Medication
Botulinum toxin-A (Allergan BV, Nieuwegein, the Netherlands) in a total dose of 30 U up to 50 U was used. BONT was diluted with saline up to 1.0 mL or 1.5 mL per gland. One single dose of BOTOX® was injected in the submandibular gland at each side divided over two sites per gland using a 25 G needle (Spinocan®).

BoNT injection procedure
The aim of our clinical study was to reduce salivary flow rate in order to reach a new balance between the quantity of secreted saliva and the swallowing capacity of the child. Therefore, only the submandibular glands were injected (see also: Fig. 1.2). The submandibular glands produce approximately 60 to 70% of the saliva when a

person is not eating or drinking. The activity of the parotids increases during gustatory stimulation, a function with which we did not want to interfere.
The children were given injections under general anesthesia because injections under local anesthesia could be too painful and frightening and would induce restlessness. Because the injections should be localized to the gland, movement of the patient could also disturb the procedure. All injections with BONT for this indication were performed as an outpatient procedure with some hours of recovery and monitoring at the daytime care-unit.
Ultra-sound guidance during the injections was performed at each occasion. The salivary glands were sonographically examined using a commercially available ultrasound system (SAL 250, Toshiba medical systems cooperation, Tokyo, Japan) equipped with a high-resolution, 7.5-MHz small-parts transducer. The transducer is positioned in such a way that injection with the needle is possible along the longitudinal axis of the transducer (Fig. 5.1), providing a quick and easy-to-perform visualization of the needle in the gland. Furthermore, ultrasound was used to position the needle at two different injection sites per gland, as well as to monitor and guide the spreading of the fluid throughout the gland.

Figure 5.1: Ultra-sound guided injection into the submandibular gland

The needle positioned along the longitudinal axis of the transducer.

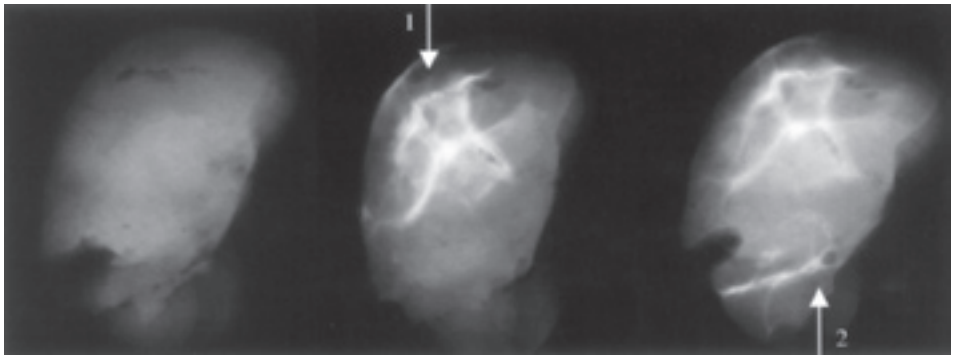
Results

In vitro study

A selection of the sequential X-rays taken during the in vitro study is shown in Fig. 5.2. The submandibular gland has been injected with Omnipaque®. The X-ray images show the result of injections in the ventral and dorsal margin of the gland. From the first injection site, several small volumes of Omnipaque®, (up to 0.75 mL) were effused into the gland showing the fluid to spread along the interlobular septa (see also: Fig 1.3) and reaching about half of the parenchyma.

More volume from the same injection site did not enlarge the spreading area. After the second injection the entire glandular parenchyma was filled up homogeneously. Based on this observation, it could be concluded that the BONT for each gland should be diluted in a volume of approximately 1 mL to 1.5 mL of saline to achieve adequate spreading of the formulation in the glandular parenchyma. Furthermore, solutions should be injected into the salivary glands at two injection sites per gland or in one deeper injection with separate small effusions while withdrawing the needle. In theory, the latter procedure may be more traumatic to the gland and may give a higher risk of bleeding.

Figure 5.2. In-vitro injections into the submandibular gland (Omnipaque®).

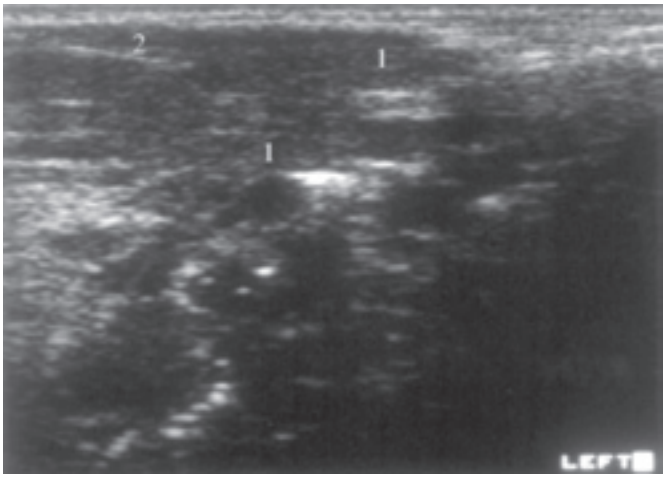


1 = 1st injection site, 2 = 2nd injection site.

In vivo study

Figure 5.3 shows an ultrasound image of the needle still penetrating the left-side submandibular gland from the ventral-medial side during injection of BONT. Figure 5.4 shows the submandibular gland as a homogenous hyperechoic structure before injection. After injection the fluid is seen as hypoechic changes in the gland. This indicates the spreading of the formulation throughout the parenchyma.

Figure 5.3. Ultra-sound image of the submandibular gland



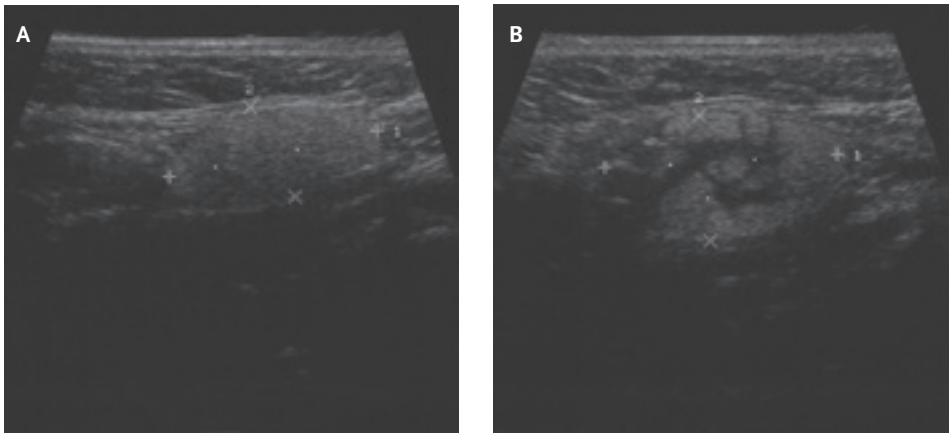
(1) during injection of BONT, the needle (2) penetrating from the ventral-medial side.

In our clinical study, 44 patients were injected according to the above-mentioned procedure, representing 88 submandibular glands. Under ultrasound guidance, we had no difficulty in localizing and identifying the submandibular gland. Besides, it was always possible to puncture the glands and visualize the needle in the parenchyma, as well as to monitor the spreading pattern of the fluid throughout the parenchyma (Fig. 5.4). The majority of the patients showed a positive effect of the BONT injections. The presentation of these data is beyond the scope of the present report, but the data indicate that the effusion of the medication was intra-glandular. These findings are in accordance with the results of an earlier reported case-series that showed a reduction of the salivary flow rate from the submandibular glands after BONT injection1.

In 88 submandibular gland injections we registered no side effect or complication of the ultra-sound-guided procedure. Following ultrasound-guided injection of a salivary gland we never observed any clinical relevant diffusion of BONT into the surrounding structures.

Since we performed the study as a daytime-care procedure, parents were asked to report every noted possible side effect. In a few cases the children complained of a temporary swelling of the submandibular gland that was experienced as uncomfortable at deglutition during a period of a few hours. Other side effects such as thickening of the saliva could be ascribed to the anti-cholinergic effect of the BONT itself.

Figure 5.4: Ultrasound images of the submandibular gland



(A) Before BoNT injection, (B) After BONT injection.

Discussion

At present, more than 50 possible indications for the application of BONT are described[5]. Bushara has suggested the hypothesis of using BONT injected into the parotid glands to treat sialorrhoea in patients with amyotrophic lateral sclerosis[3]. In the treatment of drooling Jost reported that BONT had been effective for about 4 to 7 months in five patients with Parkinson's disease who received intra-parotid injections[2]. Several other studies have confirmed the positive effect for patients with Parkinson disease[6;7]. In a preliminary investigation we found support for the assumption that BONT may be useful in the treatment of drooling in children with cerebral palsy[1].

Seven structural similar but immunologic distinct exotoxins are produced by clostridium botulinum of which Type A is widely known for its clinical application. Botulinum toxin type-A is a protein and potent neurotoxin, and appropriate care should be exercised during its preparation and use. When injecting BONT into massive structures such as the calf muscle, it is sufficient to locate the injection site by manual palpation of the muscle and perform EMG-control. When smaller anatomical structures are to be injected with BONT, it is necessary to prevent the distribution of the medication from the injection site into the surrounding structures.

Sonography, when performed by an experienced examiner, can be used to evaluate many structures and conditions in the head and neck area. When a salivary gland is punctured for cytology or injection, ultrasound guidance offers an elegant and effective method to ensure that the needle is positioned in the glandular parenchyma to avoid

lesions or effusion of the formulation in the vascular structures or the surrounding tissues.

If the parotid gland has to be injected, it is recommended to approach only the superficial part, which represents the larger part of the gland that lies close to the masseter muscle. With ultrasound guidance an erroneous injection into the masseter muscle, which would result in weakening of jaw closure, can be avoided. After ultrasound-guided injection of a salivary gland we never observed any clinical relevant diffusion of BONT into the surrounding structures. Tan et al recently reported a recurrent dislocation of the temporomandibular joint (TMJ) after BONT treatment for sialorrhoea in amyotrophic lateral sclerosis[8]. The authors describe the injection technique in which they manually palpate and locate the portion of the parotid gland lying between the ascending ramus of the mandible and the mastoid process. The depth of the injection was about 1 cm and possibly superficial enough to allow the toxin to spread in the surrounding structures. As an explanation of the TMJ dislocation, it is speculated that diffusion of the BONT into the masseter muscle could have caused weakness. That might have contributed to the clinical complaints. The specific function of the masseter muscle is to close the jaw by elevating the mandible, but it also stabilizes the TMJ as a counterpart of the posterior belly of the digastric muscle and the lateral pterygoid muscle. When, for any reason, the masseter muscle becomes flaccid and the elevation of the jaw becomes weaker, the posterior belly of the digastric muscle, together with the lateral pterygoid muscle, can bring about a moment over the TMJ and force it into anterior dislocation. To prevent an unintended deposition of BONT in the periglandular tissues, which could produce the above-mentioned side effects, the intra-glandular injections must be performed with an imaging procedure. It has been noted that anterior dislocation of the TMJ can be treated by injection of the lateral pterygoid muscle with BONT[9].

Under ultrasound guidance, Stenson's duct, emerging from the anterior border of the parotid gland, is well recognizable. This is also the place were the buccal branches of the facial nerve radiate outwards along with the duct and the transverse facial artery. BONT should not be injected in this region.

The approach of the deeper part of the parotid gland can be complicated by injections in the posterior part of the digastric muscle, the retromandibular veins, the maxillary and superficial temporal arteries or, the external carotid artery. Although ultrasound cannot adequately visualize the deeper part of the parotid in detail, the above-mentioned structures can be delineated well.

The Facial nerve is situated between the superficial part and the deeper part of the

parotid gland and should not be injected. On a transversal sonographical image this site is approximately located between the mastoid bone and the ramus of the mandible.

The submandibular gland is smaller than the parotid. There are no major structures located within the parenchyma, although some submandibular lymph nodes are within the capsule. The submandibular gland, situated between the corpus of the mandible and the medial pterygoid muscle on its lateral margin and the mylohyoid muscle on the medial side, is hard to locate accurately by palpation. The dorsal margin is grooved by the facial artery and has a close relation with the posterior belly of the digastric muscle. The inferior margin is located directly on the anterior belly of the digastric muscle. If this gland is to be injected with BONT, ultrasound guidance is needed to avoid penetration of the surrounding muscles. This might cause weakness of opening of the jaw (medial pterygoid muscles, the posterior belly of the digastric muscle) or restriction of the elevation of the oral floor and tongue during deglutition (mylohyoid muscle, the ventral part of the digastric muscle).

Because of the pharmacological properties of BONT, it has been postulated that BONT might reduce salivary flow from the salivary glands[3]. It is obvious that injections of BONT in the periglandular structures will result in a diminished effect on the salivary flow reduction and, consequently, on drooling.

The possibilities of identifying structures in the head and neck region with ultrasound techniques are well documented[10-12]. The possibility of using ultra-sound to "guide" BONT injection in the salivary glands in the treatment of sialorrhoea has already been mentioned in the literature[13;14].

Conclusion

With the procedure described, it is possible to accurately inject BONT directly into the glandular parenchyma and to visualize spreading of the fluid in the glandular parenchyma. It is found to be a safe method that guarantees an optimal clinical effect and avoids potential harmful side effects.

The available literature suggests that there is an indication to treat drooling with injections of BONT into the salivary glands[1;2;6;7;13-15]. Based on our study we recommend performing the injection procedure under ultra sound guidance.

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Chapter 6

Botulinum Toxin-A: A new option for treatment of drooling in children with cerebral palsy; the presentation of a case series.

Eur.J.Pediatr. 2001;160:509-12.

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Abstract

Drooling beyond the age of four years is pathological, particularly if it occurs in children with neurological and developmental impairment and disability. Considering the therapeutic spectrum of Botulinum toxin-A and in view of the innervation of the salivary glands, we postulated that intraglandular injections into the submandibular glands with Botulinum Toxin type-A could reduce the secretion of saliva and consequently decrease drooling. Three patients with cerebral palsy and severe drooling were selected and evaluated over a 4-month period. Under ultrasound guidance, one dose of Botulinum toxin type-A was injected bilaterally into the submandibular glands. Saliva secretion was measured at baseline and repeated four times during the following 4 months. In the three patients, maximal salivary flow rate of the sublingual and submandibular glands was reduced 51 to 63 %. The time of the maximal effect differed among the three children. The parents reported a satisfactory reduction of drooling throughout the whole study period. No objectionable disturbances of oral functions were observed. There was a mild transient thickening of saliva in one of the patients.

Conclusion: The application of Botulinum toxin type-A to the submandibular gland is a promising technique to reduce salivary flow rate and probably an alternative in the treatment of drooling in children with cerebral palsy.

Introduction

Drooling can be an important clinical, social, and emotional issue, and beyond the age of 4 years it is pathological and a clinical expression of a defect in the oral phase of swallowing[8]. Lack of control in swallowing coordination may lead to excessive pooling of saliva in the anterior oral cavity. Factors that predispose drooling in children with cerebral palsy include the degree of spasticity, a low swallowing frequency, a diminished intra-oral tactile sensitivity, and constant tongue thrusting [20]. Drooling in cerebral palsy also worsens if there is moderate or severe mental retardation. It has been reported to be a significant problem in 10% to 37,5% of patients with CP [11;22].

Salivation is mediated through the autonomic nervous system with the salivary glands functioning under a complex parasympathetic and sympathetic neural control. Parasympathetic nerves provide the main drive for the secretion of fluid by the glands. Sympathetic impulses appear to evoke specialized responses that tend to modulate the composition of the saliva. The treatment of drooling has been extensively described in the literature. The methods available for the management of drooling comprise both surgical and non-surgical options [1;2;4;6;12;13;15]. Surgical options in the treatment of

drooling are denervation of the salivary glands by transtympanic neurectomy, rerouting or ligation of the salivary duct of either the submandibular or parotid gland, and excision of one or more salivary glands [1;7;9;11;12;16]. Nerve endings of the parasympathetic postganglionic neurons system secrete acetylcholine, and blockade of these receptor sites inhibits nervous stimulation to the salivary glands. Anticholinergic drugs can be used to decrease saliva secretion. Unfortunately, due to the systemic application of the drugs a wide range of side effects are known[2;4;6;13;15]. No treatment option is universally successful, and each method has potential complications[4].

From canine studies, Shaari demonstrated that both Botulinum Toxin types A and D reduced the neural evoked production of saliva from submandibular glands[18].

Botulinum toxin type-A has the following mechanism. It binds to "SNAP-25" (25 kDa synaptosome-associated protein), a cytoplasmic protein involved in the fusion of synaptic vesicles with the presynaptic membrane. This ultimately disrupts the secretory pathway for acetylcholine and causes chemodenervation[10]. The process of denervation is reversed as the nerve end regenerates and re-innervates the target organ. Bushara has suggested the hypothesis of using Botulinum toxin injected into the parotid glands to treat sialorrhea in patients with amyotrophic lateral sclerosis[5].

In view of the pharmacological properties of Botulinum toxin type-A, we expected that injections into the submandibular glands with Botulinum toxin type-A would reduce the secretion of saliva and consequently diminish drooling. This study presents the results of a single dose injected bilaterally into the submandibular glands with Botulinum toxin type-A of three children with cerebral palsy who suffered from severe drooling.

Subjects and method

Three children with cerebral palsy and suffering from severe drooling were recruited from our outpatient clinic. Inclusion criteria (Table 1.3) were: 1) no medical condition contra-indicating therapy with Botulinum Toxin, 2) no recent (< than 6 months) injection with Botulinum toxin for other indications, 3) no known hypersensibility to BOTOX® or any ingredients of the formulation, 4) no use of anticholinergic drugs, 5) no previous surgical procedures in the oral or nasal cavity to reduce the production of saliva, and 6) a score of 3 or higher on the drooling severity and frequency scale or a score of 3 or higher on the TDS (Table 4.1 and 5.1). The characteristics of the patients are listed in Table 6.1.

Table 6.1: Patients characteristics

Patients	**1**	**2**	**3**
Sex	male	male	Female
Age (years)	13	11	13
Weight (kg.)	45	26	23
Clinical Picture	Quadriplegia	Quadriplegia	Quadriplegia
Motor expression	Spasticity/Chorea	Dystonia	Spasticity/Athetosis
Mental state	Mild retardation	Moderate retardation	Severe retardation

To classify the patients and delineate the severity of the problem, drooling was scored by means of the 'Questionnaire-based Semi-quantitative Assessment of Drooling Severity and Frequency' during the first outpatient visit[21]. All three patients had the highest score (five) on the severity scale. This score reflects that clothing; hands, tray, and objects become wet due to drooled saliva. Patient 1 scored three on the frequency scale, indicating frequent drooling. The other two patients scored four, indicating constant drooling.

We used Botulinum toxin type-A (BOTOX®; Allergan Benelux BV, Nieuwegien, The Netherlands) in a dose dependent on the child's weight. A total dose of 30 U was used for a body weight up to 15 kg, 40 U for children weighing 15 to 25 kg, and 50 U when the body weight exceeded 25 kg. These dosages were in accordance with the suggested pediatric dosing in the treatment of spasticity[17]. The Botulinum Toxin was diluted with 1.5 mL saline for each gland. From an in vitro study we noticed this to be sufficient to reach all parts of the glands. Our aim was to reduce salivary flow rate at rest in order to reach a new balance between the quantity of secreted saliva and the swallowing activities of the child. Therefore, we choose to inject the submandibular glands because these glands produce approximately 60 to 70% of the saliva whereas the parotid glands secrete about 20 -25% of the total amount of saliva when a person is at rest. Furthermore, the activity of the parotids increases during gustatory stimulation. One single dose of Botulinum toxin was injected bilaterally divided over two sites per gland by using a 25 G needle (Spinocan®). The injections were performed under general anesthesia with ultrasound guidance to precisely locate the needle within the submandibular gland.

Saliva secretion was measured from the submandibular/sublingual gland as well as

the left and right parotid gland. For this purpose, absorbent cotton rolls were used and positioned at the orifices of the salivary ducts. The orifices of the submandibular and sublingual ducts have a close anatomical relation so that separate measurement could not be obtained. The cotton rolls absorb sufficient saliva during a limited 5-minute period. The rolls were weighed before and after the procedure using an electronic scale, which was sensitive to 0.01 g. The increase in weight collected during a fixed time can be converted into mL saliva/min. Patients were evaluated at least one hour after a meal while awake and sitting erect. Before the injection each patient was screened by the speech therapist to determine base-line salivary flow rate. In the follow-up period the children were examined and salivary flow rate was measured at 2, 4, 8 and 16 weeks after the injections.

Before and after Botulinum Toxin injection, the parents were asked to complete forms containing questions about drooling, eating, drinking and daily care as a reflection of the quality of life.

The study has been approved by the Hospital Ethics in Human Research Committee.

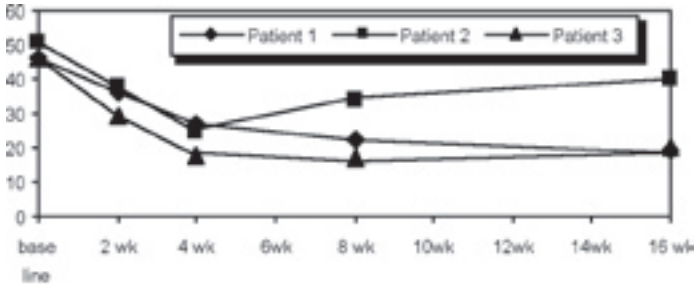
Results

The data of the salivary flow rate on consecutive measurement moments were recorded and are shown in Fig. 6.1. In all three cases, the salivary flow rate was substantially reduced on the first control visit 2 weeks after injection. The maximal salivary flow rate of the compound samples of the sublingual and submandibular glands showed a reduction of 51 to 63 %. The time of the maximal effect differed among the three children. In patient 1 and 3 reduction of the initial amount lasted throughout the study period of 16 weeks, whereas patient 2 had maximal reduction at 4 weeks.

The quality of life data collected during the follow-up period will be briefly described. Relevant observations from the parents are included in the clinical description. The clinical observations varied among the patients. Patient 1 had only mild mental retardation and his awareness that he drooled less might have ameliorated his swallowing coordination. He did not drool at all during the follow-up period. Patient 2 showed a moderate change. The salivary flow was reduced to a maximum of 51% 4 weeks after the injection. In this patient, the saliva secretion increased again before the third control visit at eight weeks following injection. He drooled less and his parents were satisfied for the whole period, because it meant that he could attend school, using only one bib. Although patient 3 never stopped drooling during this study, there was an impressive reduction. In the questionnaires the parents responded that there was also

a major reduction of drooling during the night when the pillow only became damp. This result was probably related to the favorable recumbent posture in combination with the reduction of saliva secretion of 61% and 63 % found at 4 and 8 weeks respectively after injection. For all patients, the left and right parotid glands showed no change in secretion activities during the 16 weeks following the single dose. There were no objectionable disturbances of oral function observed in all three patients. Patient 3 had a mild, transient thickening of saliva, which was treated for three days with a mucolytic drug.

Figure 6.1: Submandibular salivary flow (mL/min), left and right side together



Discussion

This study investigates the effect of a single dose of Botulinum toxin type-A on reducing salivary flow rate in 3 children with cerebral palsy. In all 3 children the maximal reduction was greater than 50 %.

Generally the effect of Botulinum toxin in the treatment of spasticity lasts about 3 to 4 months[19]. In the treatment of drooling, Jost describes that Botulinum toxin had been effective for about 4 to 7 months in five Parkinson patients treated with intra-parotid injections[14]. Our study shows that the submandibular gland reacted similarly. For only one patient the reduction in salivary flow rate was less than 4 months. Possible explanations are: 1) inappropriate injection site, 2) a disproportion between the injected volume of diluted Botulinum toxin and the size of the glands, or 3) a short lasting effect of the Botulinum toxin.

Patient 2 reacted relatively short, possibly related to a quick induction of nervous sprouting. The parents of this patient reported they were satisfied about the lesser amount of drooling during whole the study period. In our patients, general anesthesia was used to perform the procedure. However, it is conceivable that if one gets more

familiar with the technique of intraglandular injections under ultrasound guidance, the injections can be done with just sedation instead of anesthesia. We intended to diminish salivary flow rate from the submandibular glands and leave the parotid glands to produce saliva when the person eats and drinks.

This study supports the hypothesis that injections with Botulinum toxin type-A into the submandibular glands will decrease salivary flow rate for an acceptable period. The duration of the effect appears to vary. Questions remain about several subjects such as the most appropriate dose, the effect of Botulinum toxin injections on the composition of saliva, and the duration of the effect. Further research is required to evaluate the effectiveness of intraglandular application of Botulinum toxin in either the parotid glands or in the submandibular glands. A comparative prospective study with a larger number of patients is needed together with a relevant quality of life study.

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Chapter 7

The effect of Botulinum neuro-toxin on salivary flow rate

Neurology (2004): In press

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Abstract

Background: To investigate the effectiveness of Botulinum neurotoxin type-A (BoNT) in reducing salivary flow rate in children with Cerebral Palsy (CP) suffering from severe drooling. During a controlled clinical trial, single-dose BoNT injections into the submandibular salivary glands were compared to scopolamine treatment.

Methods: Forty-five school-aged children were included. Salivary flow rates from all major glands were obtained at baseline and compared to measurements during the interventions. Basic statistics consisted of analysis of difference scores.

Results: Compared to baseline, the mean decrease in submandibular flow was 24.7 % during scopolamine and 42.4 % following BoNT injections. The difference scores were statistically significant with maximum reductions 2, 4 and 8 weeks following BoNT. Of all children, 94.9 % responded during scopolamine. Response rates for BoNT varied from 69.2% two weeks to 48.7% twenty-four weeks after injection, the end of the study. Four patients discontinued scopolamine therapy because of side effects. Only incidentally mild side effects were reported from BoNT.

Conclusion: Intra-glandular BoNT injections significantly reduce salivary flow rate in the majority of drooling CP children demonstrating high response rates up to 24 weeks. The procedure is simple to perform, effective and safe when ultrasound guidance is used. This is the first controlled trial comparing the efficacy of Botulinum toxin to another anticholinergic agent. The anticholinergic effect of BoNT exceeds that of scopolamine. Since anticholinergic drugs are frequently contra-indicated because of side effects, BoNT injections offer an alternative in the treatment of drooling. BoNT could be beneficial to a broader group of patients, both children and adults, if a reduction of salivary flow is needed in the treatment of drooling.

Introduction

The efficacy of Botulinum toxin (BoNT) injections in the salivary glands to treat drooling is promising[1-3]. For safe injections and optimal results ultrasound guidance is needed. In addition, anesthesia is required when children are treated[4,5]. From the pharmacological profile of BoNT an appreciable anticholinergic effect can be expected[6,7]. In particular, type-A toxin cleaves SNAP-25, an enzyme involved in the release of acethylcholine at the presynaptic membrane of parasympathetic nerves. However, its capability to reduce the salivary flow rate has not yet been established. Uncertainty still exists about the efficacy and duration of the effect. Preliminary reports, presenting case series or small cohort studies, describe different techniques for evaluation[1-3,8]. The reader cannot conclude

whether the use of BoNT would be an improvement over other interventions. BoNT is an anticholinergic agent. The use of other anticholinergic drugs to treat drooling has been reported repeatedly in the literature and an extensive clinical practice exists in the application of this medication.
The objective of this study was to investigate the effectiveness of BoNT to reduce salivary flow rate in drooling children with cerebral palsy (CP). A controlled clinical trial has been performed in which BoNT injections of the submandibular glands were compared to treatment with scopolamine. The results of quantitative measurements of salivary flow rates are summarized. The nill hypothesis that 'there would be no difference in effectiveness of flow reduction between scopolamine and BoNT', was tested.

Method and material

Patients

Fifty-three consecutive patients with the diagnosis CP were screened in the outpatient clinic between January 2000 and November 2001. Forty-five severely drooling children were included, according to the criteria as tabulated in Table 1.3.
All drugs used were carefully evaluated to assess their influence on saliva secretion. Continuous use of anticholinergic drugs or benzodiazepines was not allowed. In particular clonazepam was a reason for exclusion. Throughout the study no change in medication was allowed. Medication to treat drooling had to be stopped at least three months prior to participation. All possible adverse effects and risks related to the study were explained to the parents and written informed consent was obtained. The Hospital's Human Research Committee approved the study.

Design

In this controlled "open-label" clinical trial, salivary flow rate measurements from all major salivary glands were performed during scopolamine application that were compared to the results of BoNT injections into both submandibular glands. An independent observer assessed the primary outcome parameter (salivary flow rate) blinded for the status of the participating patients. This was achieved by varying baseline measurements among the patients according to a predetermined schedule.
In view of side effects the protocol anticipated that some of the patients might not complete the scopolamine period. If scopolamine was used less than 48 hours, the subject was considerate a dropout. If scopolamine was discontinued after 48 hours,

the subject remained in the study provided a salivary flow measurement was obtained within the first 24 hours after discontinuing the therapy.

Procedures

Scopo-derm TTS® 1.5 (Novartis Consumer Health BV, Breda, the Netherlands), a sticky plaster containing 1.5 mg of the anticholinergic drug scopolamine, was placed behind the ear for a maximum of 10 to 14 days. After clear instructions, parents were asked to fill out a daily form to register side effects. Assessment was scheduled on the tenth day with the plaster still in place. After a washout period of 2 to 4 weeks, the child was admitted for outpatient treatment. Under general anesthesia a single dose of Botulinum toxin (Botox®, Allergan, Nieuwegein, the Netherlands) was injected bilaterally in the submandibular glands, using a 1 ml syringe. The total dosage, divided between the left and right gland, depended on the child's weight: 30 U for children weighing less than 15 kg, 40 U for children with a body weight between 15 and 25 kg, and 50 U for children weighing more than 25 kg. On injection, each dose was fractionated and divided over minimally three sites in the gland. To locate the glands, ultrasound guidance was performed using a system (SAL 250: Toshiba medical sysytems cooperation, Tokyo, Japan) equipped with a 7.5-MHz transducer[4]. The submandibular glands were injected as it is generally accepted that these glands produce 60 to 70% of secreted resting saliva[9]. Saliva produced during eating and drinking is mainly produced by the parotid glands with which we did not want to interfere.

Follow-up measurements were planned at 2, 4, 8, 16, and 24 weeks after BoNT. Parents were asked to register side effects in a diary.

Prior to the assessment the mouth was cleaned and dried by gauze. In order to measure salivary flow rate the 'swab method' was used during which absorbent cotton rolls (Salivette®, Sarstedt B.V, Etten-Leur, the Netherlands) were placed directly at the orifices of the submandibular, sublingual, and parotid glands for a 5-minute period. The procedure was always executed by the same speech therapist in the same environment. Patients were evaluated in the morning after at least 1 hour of starvation and while awake and sitting erect. Special attention was paid to the body posture with the head in an upright position. The flow rate was calculated by the formula: Salivary flow rate [mg/min] = (weight increase of rolls [mg] / time of collection [min]). Since the specific gravity of saliva is 1.0 the results were converted to ml/min. The procedure was repeated after 30 minutes. The mean of the two measurements was the outcome parameter.

Because of the close anatomical relation between the sublingual and submandibular glands, separate flow rates could not be obtained. The compound salivary flow from these two glands is referred to as submandibular flow (SubFl). The salivary flow from the right parotid (PaRFl) and the left parotid gland (PaLFl) were also assessed. The 'total salivary flow' (TSFl) was the summation of SubFl, PaRFl and PaLFl.

Statistics

A power analysis was performed to calculate the required number of patients. Approximately 40 subjects were needed to reach a power of 80% with an alpha of 0.05. The difference between the two episodes of treatment had to be at least 1 SD. Assuming a dropout percentage of 7%, the inclusion of 45 subjects would have sufficient power. Because of the complexity of the design and vulnerability of the patients, missing data were inevitable. For this reason data were adjusted by 'last observation carried forward' (locf) and by a 'worst case scenario' (wcs) system. In the wcs procedure all missing data were replaced by baseline values. In this way the difference in potential effect for both therapies was "reduced" by introducing a bias towards zero.

A MANOVA was executed to identify patterns of response using a within-subjects design with the subsequent measurement moments as the variables. In addition, paired samples t-tests were done for SubFl as well as TSFl data to analyze difference scores in flow rate.

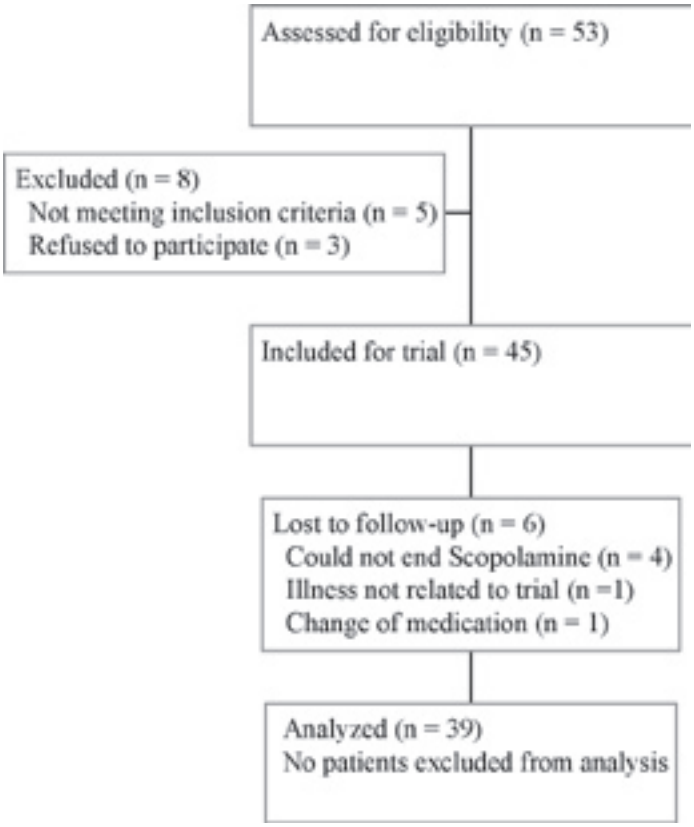
In order to quantify the measurement error of the swab method, the within-subjects standard deviation (SW) was estimated from repeated baseline measurements of each patient that were performed under standardized conditions10. The biological variation and the between-subjects variation in salivary flow rate and the error in the measurement procedure itself influence the magnitude of the SW. For the clinician, the SW clarifies whether a change in flow rate is the result of measurement error alone or the outcome of an applied intervention. In this study, success to either scopolamine or BoNT treatment was defined as a decrease in SubFl of more than 1.0 SW. For all statistics a level of significance with a p-value ≤ 0.05 was obligatory.

Results

Forty-five children were included (Fig.7.1), 28 male, 17 female, age 3-17 years (mean 9.5, SD 3.7). No child had to be excluded because of use of medication. Of all patients, 21 did not use medication, 4 patients incidentally used benzodiazepines to treat epileptic seizures, and 2 patients stopped medication that was given to treat drooling. None

of the subjects had Botulinum toxin before. By the end of the trial six dropouts had occurred: 4 patients could not fulfill the scopolamine period, 1 changed anti-epileptic medication, and 1 did not attend the required measurements because of intercurrent illness not related to the trial. The results of 39 patients were analyzed according to an "intention to treat model".

Figure 7.1: Flow diagram of subject's progress through phases of the trial



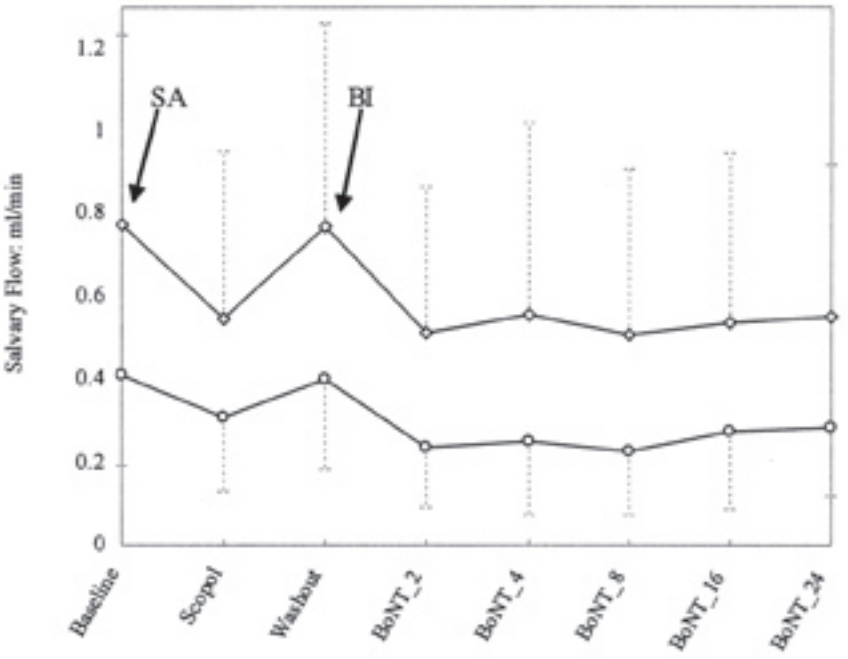
There were no missing values in the baseline data. Of all other measurement, 21 missing values representing 6.7% of the total, were estimated as follows (number of missing/number of patients): scopolamine (4/39); washout (1/39); BoNT-2 (2/39); BoNT-4 (9/39); BoNT-8 (2/39); BoNT-16 (2/39); BoNT-24 (1/39). Primary analyses were done with the locf data. Descriptive statistics of the consecutive measurement moments are tabulated (Table 7.1).

Table 7.1: Descriptive statistics at baseline and subsequent follow-up measurements

	Mean	SD	Median
Baseline	.41	.22	.37
Scopolamine	.31	.18	.28
Washout	.40	.22	.37
BoNT-2	.24	.15	.22
BoNT-4	.25	.18	.20
BoNT-8	.23	.15	.20
BoNT-16	.27	.19	.24
BoNT-24	.28	.16	.28

Compared to baseline, the mean salivary flow rates of SubFl as well as TSFl decreased during scopolamine application and after BoNT injections, as is shown in Fig. 7.2.

Figure 7.2: Mean Salivary Flow at subsequent measurement moments (Locf data)



locf = last observation carried forward, SubFl: Submandibular flow (-○-), TSFl: Total Salivary Flow(-◊-), SA: Scopolamine application, BI: BOTOX Injection,
Baseline: Measurement at baseline, Scopol: Measurement during scopolamine application, Washout: Measurement after Washout, BoNT-X: Measurements at subsequent moments (Wks) following BoNT injections.

With the SubFl at each moment in time defined as the within-subjects variable a MANOVA, with a repeated measurements design was executed to evaluate the pattern of response of the assessments during the trial (Hotelling's trace: F=13.83; df (7.32); $p < 0.001$). An effect over time was found as depicted in the Fig. 7.2 and described in further detail by analysis of difference scores (Table 7.2).

The procedure was repeated for the TSFl (Hotelling's trace: F=7.892; df (7.32); $p < 0.001$). Because the between-subjects variation was larger for the TSFl data, a natural log-transformation was done to stabilize the variance and patterns over time. A MANOVA was executed (Hotelling's trace: F=15.029; df (7.32); $p < 0.001$). Because the graphical pattern showed great resemblance to the original TSFl data it was concluded that the curves in the

Table 7.2: Mean change of submandibular flow as a result of interventions (N = 39)

	Locf data (mL/min.)			
Measurements	**Mean change from baseline (SD)**	***p* value**	**Mean change from washout (SD)**	***p* value**
Scopolamine	0.10 (0.16)	0.001		
BoNT-2	0.17 (0.17)	0.001	0.16 (0.16)	< 0.001
BoNT-4	0.16 (0.19)	0.001	0.15 (0.20)	< 0.001
BoNT-8	0.19 (0.16)	0.001	0.17 (0.17)	< 0.001
BoNT-16	0.14 (0.15)	0.001	0.12 (0.20)	0.001
BoNT-24	0.13 (0.17)	0.001	0.11 (0.21)	0.002

N: number of patients, Locf: last observation carried forward,
SD: Standard deviation, BL: Baseline,
BoNT-X: Measurements at subsequent moments (wks) following BoNT injections

Fig. 7.2 were comparable. Compared to baseline, the TSFl changed in the same direction over time as the SubFl with reduction during scopolamine application, return to baseline level during washout, and a second decrease in salivary flow rates following BoNT injections.

If the washout period was chosen properly the salivary flow rates after 'washout' of scopolamine should be in the same range as baseline measurements. A paired samples t-tests was performed to calculate the difference between baseline SubFl (locf data) and washout (mean difference = 0.0119 mL/min; SD = 0.2165; 95% confidence

interval of the difference -0.0582 to 0.0821; $p = 0.733$). No significant difference was found, indicating that the length of the washout period was sufficient. This finding minimizes the probability of a carry-over effect from scopolamine treatment to the BoNT injection period.

Compared to baseline SubFl showed a mean reduction of 24.7 % during scopolamine and a mean reduction of 42.4 % 2 weeks after BoNT. Table 7.2 presents the differences and significance between baseline measurements and the measurements after treatment. The greatest reductions in salivary flow were achieved 2, 4, and 8 weeks following BoNT. The SubFl appeared to increase slightly after BoNT-8 but remained significantly different from baseline.

Further analyses of SubFl were performed to investigate the mean differences between the individual BoNT assessments and scopolamine (Table 7.3). BoNT measurements 2, 4 and 8 weeks after injections, showed significantly greater reduction compared to scopolamine. Between the eighth and the sixteenth week after BoNT this significance disappeared.

Table 7.3: Mean change of submandibular flow between interventions (N = 39)

	Locf data (mL/min.)	
	Mean change from scopolamine to BoNT (SD)	***p* value**
Sc: BoNT-2	0.0725 (0.13)	0.01
Sc: BoNT-4	0.0607 (0.15)	0.14
Sc: BoNT-8	0.0828 (0.13)	< 0.001
Sc : BoNT-16	0.0371 (0.15)	0.129
Sc : BoNT-24	0.0258 (0.16)	0.327

N: number of patients, Locf: last observation carried forward, SD: Standard deviation, BL: Baseline, BoNT-X: Measurements at subsequent moments (wks) following BoNT injections Sc: Scopolamine.

Analysis of "worst case scenario" data did not lead to different results comparing baseline to both treatments. However, no significant difference in salivary flow reduction could be found comparing scopolamine to BoNT.

In this study the within-subjects standard deviation (SW) of the baseline measurements was 0.11 ml/min (see: methods), which is acceptable regarding the mean SubFl of 0.40ml/min. Success to scopolamine, was achieved in 94.9 % of the children. Success

rates for BoNT were: BoNT-2 (69.2%), BoNT-4 (64.1%), BoNT-8 (61.5%), BoNT-16 (48.7%) and BoNT-24 (48.7%). McNemar test was used to compare the response rate after scopolamine to the response rate 2 weeks after BoNT ($p = 0.002$). In favor of scopolamine, there appeared to be a significant difference in the number of patients that responded according to our definition.

Adverse effects during application of scopolamine were reported in 82.2% of cases. Side effects due to scopolamine became apparent within the first three days of administration and several patients complained of more than one symptom. Five patients (11.1%) had 'mild', fourteen patients (31.1%) had 'moderate', and 18 patients (40%) had severe side effects. Most often reported adverse effects were xerostomia in 66.7% of cases, restlessness 35.6%, somnolence 35.6%, blurred vision 20%, and confusion in 20% of cases. No morbidity was seen in relation to the general anesthesia. Following BoNT injections, incidental side effects were reported. Two patients (5.1%) had a transient flu-like syndrome lasting for less than 2 days. Another 2 patients complained of mild difficulty of swallowing. This was ascribed to local swelling, which subsided in a few hours. In one case moderate difficulty with swallowing developed after one week and was present for 10 days. It was theorized that this could be the result of diffusion of Botulinum toxin into the surrounding muscles, which would explain the one-week interval for the symptoms to develop. However, when one considers the physiological action and the process of re-innervations, it is difficult to understand how the problem could disappear within 10 days.

Discussion

Persistent drooling is a serious medical and social problem. The general opinion still is that neither conservative therapy (speech therapy, behavioral therapy, drugs) nor surgical interventions are universally successful[11-13]. Intra-glandular Botulinum toxin injections in the salivary glands have been suggested in the past few years[2,3,14,15].

This is the first controlled clinical trial that evaluated the reduction of the salivary flow rate by comparing the efficacy of Botulinum toxin to another anticholinergic agent. The effect of BoNT on the reduction of submandibular salivary flow exceeded that of scopolamine. Compared to baseline, the mean reduction following BoNT injections was 42.4% versus 24.7% during scopolamine. This reflects the explicit anticholinergic effect of BoNT.

The number of responders was calculated according to our definition of therapeutic success. Success rates were high with the outcome in favor of scopolamine

(scopolamine: 94.9%, BoNT_2: 69.2%). In theory the difference in response rate can be explained in several ways: 1) the reaction to BoNT may be dose related. We did not investigate this because dose finding was not an aim of this study, 2) BoNT (or part of it) was not injected in the gland. However, ultrasound guidance assured adequate delivery and 3) immunity existed for BoNT. We did not rule out this possibility. However, the risk of neutralizing anti-BoNT type-A antibodies was low because none of these patients had previously been treated with Botulinum toxin.

Unless the above-mentioned, the number of responders to BoNT remained well throughout the 24-week duration of the study. This long-term reduction of the salivary flow from one of the major salivary glands is a promising finding since Botulinum toxin is known to work for 9 to 12 months in other conditions involving the autonomous nervous system, for example hyperhidrosis[16,17].

The study was executed as an "open label" trial because the applied interventions could not be blinded. The possibility of a carry-over effect necessitated a strict sequence in the treatment order: scopolamine prior to Botulinum toxin. The washout period of scopolamine appeared to be sufficient at analysis of the results.

Using the swab method for salivary flow measurement, oral stimuli by the dental rolls cannot be avoided which may partly explain the between-subjects variation in both the SubFl and the TSFl. The capability to react to intra-oral tactile stimuli with a higher level of secretion is more explicit in the parotids. This probably is a reason why TSFl, including the parotids, showed a greater variation. Nevertheless, the data of SubFl and TSFl demonstrated a similar trend, which is in line with the fact that the parotids, the sublingual and the minor salivary glands have a limited contribution to the non-stimulated saliva production.

A complete blockage of SubFl was not achieved. This might be explained by the fact that parasympathetic innervations as well as ortho-sympathetic innervations stimulate salivary secretion. In canine studies it was demonstrated that after complete anticholinergic blockage of the glands with atropine, a maximum of 76% of submandibular salivary flow reduction was achieved[7]. Therefore, it is not likely that in man full blockage of salivary flow would be achieved, by applying anticholinergic treatment.

Averse reactions to scopolamine occurred in 82.2% of cases. In approximately 9 % of cases, treatment had to be terminated due to side effects, which explained 4 out of 6 dropouts from the study. BoNT injections were given under general anesthesia of which the potential risks should not be neglected. This should be weighed against the

possible adverse effects that are to be encountered when using scopolamine (or other anticholinergic drugs) for a longer period. Following BoNT only mild side effects were registered. However, a temporary disturbance in swallowing was reported in 7.6 % of cases that required no additional measures.

No decisive conclusion could be drawn from the literature regarding the optimal effective dosage of BoNT for injection into the salivary glands. Determining the optimal effective dose was not an objective of the present study. The dosages used in this study, appearing to be effective, were derived from existing guidelines for intramuscular injections and are far within the safety limits of Botox®[18]. The volume in which the BoNT should be diluted was based on the findings of an in-vitro study regarding the spread of BoNT in the gland after injection[4]. Recent reports mention successful treatment of drooling using lower dosages of Botox®[2,3]. Taking this into account it is not likely that too low dosages were used in our study.

Considering the side effects as observed of scopolamine, BoNT injections are more favorable when salivary flow reduction is needed in the treatment of drooling. Although temporary, salivary flow reduction following BoNT injections is of satisfying duration for the responders. A disadvantage is the need for anesthesia in the treatment of children. Surgery, providing a definite solution, also has to be considerate as a potential alternative. Further research is needed to investigate the long-term outcome of BoNT injections into the submandibular glands also in combination with the parotid glands. Dose-finding studies are warranted. The technique of intraglandular BoNT injections has to be compared to surgical interventions. In this respect it seems of great importance to define age groups or specific diagnoses in both children and adults that form particular indications for one or the other approach.

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Chapter 8

The effect of Botulinum toxin in the treatment of drooling: A controlled clinical trial

Pediatrics 2004 Sep; 114(3):620-7

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Abstract

Objective: To investigate the clinical effectiveness of Botulinum neurotoxin type-A (BoNT) to reduce drooling in children with cerebral palsy (CP).

Methods: A controlled clinical trial was performed in which the results of single-dose BoNT injections in the submandibular glands were compared to treatment with scopolamine. Forty-five children who had CP and experienced severe drooling were enrolled. Drooling severity was measured at baseline, during application of scopolamine and at different intervals after BoNT injections up to 24 weeks, using the Drooling Quotient (DQ), the Teacher Drooling Scale (TDS) and Visual Analog Scales (VAS).

Results: Drooling was reduced during scopolamine application as well as following BoNT injections. Compared with baseline, the mean DQ showed a significant decrease throughout the study. Greatest reductions were achieved 2 to 8 weeks after BoNT injection. No significant differences were found between scopolamine measurements and those up to 24 months after BoNT injection. Using VAS, parents recorded the effect on drooling in which significant differences were found between baseline VAS score and all follow-up assessments. According to our definition of "success to therapy", demanding a 2-point decrease on the TDS, 61.5 % of patients responded to BoNT injections. Analysis of the DQ demonstrated a response rate of 53% of the patients to scopolamine and 48.7% to BoNT until 24 weeks after BoNT injections, the actual duration of this study. As a reaction to scopolamine, 71.1% of the patients had moderate to severe side effects. Only non-severe, incidental side effects were reported following BoNT injections.

Conclusions: During scopolamine application as well as following intra-glandular BoNT injections, a clinically relevant reduction of drooling was achieved in children with CP, demonstrating maximum effect 2 to 8 weeks after injections. This is the first controlled clinical trial that confirmed a significant effect of BoNT injections in the treatment of drooling. General anesthesia was needed for all children. BoNT injections show fewer and less serious side effects than transdermal scopolamine treatment.

Introduction

Drooling is an important clinical problem in ~ 10% to 38% of cerebral palsy patients[1-3]. Insufficient control of the coordinate mechanism of orofacial, palatolingual, and head and neck musculature results in excessive pooling of saliva in the anterior part of the oral cavity and unintentional saliva loss[4]. Hypersalivation is generally not the case

in children with CP. Direct saliva collection can be performed by the swab method in which absorbent cotton rolls are placed directly at the orifices of the glands for 5 minutes. The flow rate can be calculated by the formula: Salivary flow rate [mg/min] = (weight increase of rolls [mg] / time of collection [min])[5;6].

The clinical evaluation of drooling severity and frequency is difficult because of within-subjects fluctuation during the day and a large between-subjects variation. Several systems have been used and advocated for assessment of the extent of drooling,. Since its introduction, various modifications of the Drooling Quotient (DQ) have been used[7;8-13]. The DQ is a validated semi-quantitative, direct observational method (see: methods)[7;14]. Rating scales such as the Teacher Drooling Scale (TDS) have been designed to assess drooling severity and frequency. The TDS is a useful tool for out-patient visits[15].

The management of drooling remains a problem. Despite effective treatment modalities to diminish saliva production drooling may persist. Many factors contribute to the saliva passage from the oral cavity to the esophagus, such as the child's mental abilities, the cognitive awareness of social norms, an intact swallowing mechanism, oral sensibility, lip closure, and the ability to hold the head in an upright position. In addition, variables that may influence salivary flow rate are medication, circadian rhythms, prestimulation, gender, age, psychological effect, and general health[16-21]. The effective reduction of saliva production is relevant to the patient only when the treatment leads to a clinically apparent diminished drooling.

Conservative treatments as well as surgical procedures all have their limitations[22]. Recent reports suggested Botulinum neurotoxin type-A (BoNT) injections into the salivary glands as an option for treatment of drooling[6;9;10]. These reports are case series and small cohort studies lacking the power to prove the efficacy of BoNT injections. Ellies et al studied a larger population and concluded that the BoNT effect lasted for ~ 2 to 3 months[23]. From the pharmacological profile of BoNT, an appreciable anticholinergic effect can be expected. In particular, type-A toxin cleaves SNAP-25, an enzyme involved in the release of acethylcholine at the presynaptic membrane of parasympathetic nerves. In this way, a temporary denervation of the target organ is established. Botulinum toxin is known to give clinically relevant results for 9 to 12 months in other conditions involving the autonomic nervous system, for example hyperhidrosis[24;25]. Although BoNT has been suggested for clinical use in the treatment of drooling, uncertainty remains about the clinical effect and duration.

In this study, a controlled clinical trial on the treatment of drooling has been

performed in which BoNT injections in the submandibular glands were compared with scopolamine treatment. Difference scores of semi-quantitative measurements of drooling (Drooling Quotient; Teacher Drooling Scale; Visual Analog Scales) were analyzed. The null hypothesis that 'the effect on drooling would not differ between scopolamine and BoNT' was tested.

Method and material

Patients

Forty-five children with the diagnosis CP were recruited from the outpatient clinic and enrolled in the study between January 2000 and November 2001. Consecutive subjects were included during a qualification period in which inclusion criteria and exclusion criteria were examined (Table 1.3).

A score of 3 or higher on the TDS (Table 8.1) was mandatory to be included in the study[15]. All drugs used were carefully evaluated to assess their influence on saliva secretion.

Table 8.1: Teacher drooling scale

1	No drooling
2	Infrequent drooling; small amount
3	Occasional drooling; intermittent all day
4	Frequent drooling; but not profuse
5	Constant drooling; always wet

Drugs to treat drooling had to be stopped at least three months before participation. Throughout the study, no medication that could influence the severity of drooling was allowed. No requirements were set with regard to the child's level of mental development.

Possible adverse effects and risks related to the interventions during the study were explained to the parents. Written informed consent was obtained. The Hospital's Human Research Committee approved the study.

Study Design

The study was executed as a controlled, open-label, clinical trial. The difference between the 2 episodes of treatment had to be at least 1 SD. Drooling evaluation (see

Procedures) was performed during baseline, scopolamine application, and after BoNT injections into the submandibular glands. The sequence of interventions had a fixed order: scopolamine before BoNT. This was chosen because the washout period of scopolamine is known, whereas the duration of the supposed effect of BoNT needed to be determined. An independent employee assessed the primary outcome parameters blinded for the status of the participating patients, which was achieved by varying the number of baseline measurements among the patients according to a predetermined schedule.

In view of side effects of scopolamine, the protocol anticipated that some of the patients might not complete the scopolamine period. When scopolamine was used for <48 hours, the patient was considerate a dropout. When scopolamine was discontinued >48 hours after start, the patient remained in the study, provided a control measurement was obtained within the first 24 hours after discontinuation of the therapy.

Patients returned for follow-up measurements at 2, 4, 8, 16 and 24 weeks after BoNT injections. Patients had to have undergone at least 1 of the scheduled investigations at 2, 4 or 8 weeks. At least 3 of 5 visits within the first 24 weeks after BoNT injections had to be conducted.

If a patient was excluded during the use of scopolamine or during the washout period, it was planned to contact the parents by telephone after 2 and 4 weeks to check for adverse effects or other complaints. Dropouts after the BoNT injections were to be contacted monthly until 24 weeks post injection.

Procedures

A scopolamine patch (Scopo-derm TTS®, Novartis Consumer Health BV, Breda: The Netherlands) was placed behind the ear and changed within every 72 hours. An assessment was scheduled on the 10th day with the 4th plaster in situ being applied no longer than 48 hours before. After a washout period of 2 to 4 weeks, the child was admitted for outpatient treatment. Using general anesthesia for all patients, a single dose of Botulinum toxin (Botox®, Allergan, Nieuwegein: The Netherlands), reconstituted with 0.9% sodium chloride solution, was injected bilaterally in the submandibular glands using a 25 G needle (Spinocan®) and a 1 mL syringe. Weight-dependent dosages were injected in each gland: 15 U/gland for children who weighed <15 kg, 20 U/gland for children with a body weight of between 15 kg and 25 kg, and 25 U/gland for children who weighed >25 kg. On injection, each dose was fractionated and divided over minimally 3 sites in the gland. Ultrasound guidance was performed

using a system (SAL 250: Toshiba medical systems cooperation, Tokyo, Japan) equipped with a 7.5-MHz transducer. Only the submandibular glands were injected. It is generally accepted that these glands produce 60 to 70% of secreted resting saliva when the individual is not eating or drinking[26]. Saliva that is produced during eating and drinking is produced mainly by the parotid glands, with which we did not want to interfere. The sublingual glands, contributing up to 5% to the total saliva production, were not treated.

After BoNT, parents were asked to register all possible side effects in a diary. These were discussed during outpatient visits.

Assessment of drooling

The DQ and VAS served as the primary outcome measures for this study. The TDS, scored on an ordinal scale, was used to give supportive evidence for the efficacy of BoNT.

The DQ was scored according to its original design during two periods of 10 minutes separated by a 60 minute break[7]. An episode of drooling was defined as new saliva present on the lip margin or dropping from the chin[12]. Every 15 seconds (40 observations in 10 minutes) the presence or absence of drooling was assessed. Patients were evaluated at least one hour after a meal while awake and sitting erect. Two speech therapists were especially trained to execute the measurements. Separate observations were made during different activities: 1 with the child watching TV and 1 during an activity, as chosen by the child, that demanded a higher level of concentration or physical effort. The mean of the 2 observations was used for analysis to provide an outcome on a numerical scale.

The DQ was expressed as a percentage estimated from the ratio of observed drooling episodes and the total number of observations (DQ [%] = 100 X number of drooling episodes/40)[8].

DQ assessments were made at baseline, during the use of scopolamine, at washout after ending scopolamine therapy, and at regular intervals after BoNT injections (2, 4, 8, 16, and 24 weeks).

After receiving specific instructions, parents filled out Visual analog scales (VAS) in order to investigate therapy results as experienced in the home situation. Scales of exactly 10 cm without visible subdivisions were presented on which the average degree of drooling severity during the 10 to 14 days before assessment had to be indicated. A mark at the left end represented severe drooling; a mark at the right end meant

no drooling. An independent employee scored the VAS with a ruler in millimeters, resulting in a number ranging from 0 to 100, which was handled as a parametric variable. VAS assessment was made at baseline, during the use of scopolamine and at regular intervals after BoNT injections (4, 8, 16, and 24 weeks).

The TDS (Table 8.1) was used to assess the degree of drooling by interviewing the parents or caregivers during outpatient visits[15]. Assessments of TDS were made at baseline and after BoNT injections (8 and 24 weeks). Before analysis of the data, a significant reaction to therapy was defined as a 2-point improvement on the TDS (range 1-5, Table 8.1). The outcome after BoNT injections is only used to support the findings in the DQ and VAS data.

Statistics

A power analysis was performed before start of the study. Approximately 40 subjects were needed to reach a power of 80% with an alpha of 0.05. The difference between the 2 episodes of treatment had to be at least 1 SD. Assuming a dropout percentage of 7%, the inclusion of 45 subjects was sufficient. Because of the complexity of the design and vulnerability of the patients, missing data were inevitable. For this reason data were adjusted in 2 ways: 1) by carrying the last observation forward (clof) and 2) by a worst-case scenario (wcs) system. In the wcs procedure all missing data were replaced by baseline values. In this way the effect difference between the therapies was "reduced" by introducing a bias towards the null. The outcomes of both approaches were compared.

All statistical procedures were carried out with SPSS/pc+$^{(tm)}$ (version 9.0; SPSS, Inc, Chicago, IL). Data analysis included descriptive statistics; multivariate analysis of variance (MANOVA) of repeated measurements to identify patterns of response over time, using a within-subjects design with the measurement moments as the variables; and paired-samples t tests to analyze differences of paired observations (DQ and VAS) at subsequent measurements. In addition, success of therapy for either scopolamine or BoNT was defined as a decrease in DQ of at least 50% of the patient's baseline value. Frequency analyses were performed to determine the percentage of responders in the population. A Wilcoxon signed-ranks test was used to analyze changes in TDS (ordinal scale). For all statistics a level of significance with a one-sided p-value $\leq .05$ was mandatory.

Results

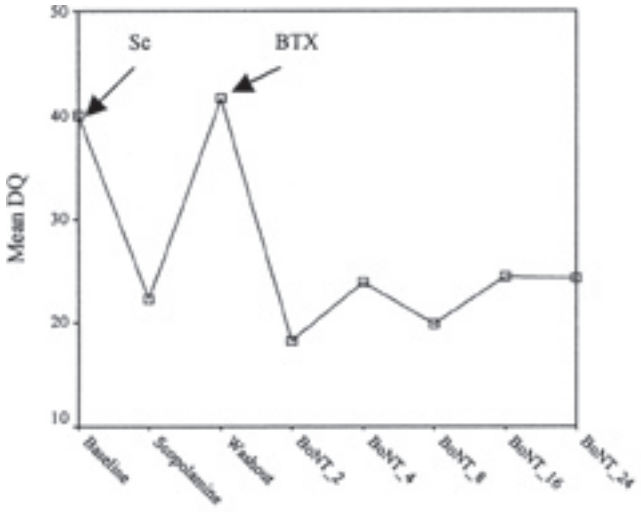
Forty-five children were included; 28 boys and 17 girls (age: 3-16 yrs; mean: 9.5; SD: 3.7). Eight were ambulant without aid, 37 had wheelchairs, 22 could not talk, 29 attended a special education school, and 14 went to a daycare center for mentally handicapped children. Thirty-four children had a mental retardation with a developmental level <6 years as determined by psychological investigation.

None of the subjects was treated with Botulinum toxin before. By the end of the trial, 6 dropouts had occurred: 4 patients could not fulfill the scopolamine period, 1 changed anti-epileptic medication, and 1 did not attend the required measurements because of an intercurrent illness not related to the trial. The results of 39 patients could be analyzed.

DQ

In the first instance, analyses were executed with 'clof' data. Descriptive statistics of the consecutive measurement moments showed that, compared with baseline, the mean DQ decreased during scopolamine application as well as after BoNT injections, which is shown in Figure 8.1.

Figure 8.1: Mean drooling quotient in time



Sc = Application of Scopolamine; BTX = Injection of Botulinum Toxin
BoNT = Botulinum toxin; BoNT-X = interval in weeks after injections; DQ = Drooling Quotient

With the DQ at each moment in time defined as the within-subjects variable, a MANOVA with a repeated measurements design was executed to evaluate the pattern of response during the trial (Hotelings trace: F=12.79; df (7.00); p = .000).

An effect over time was found as depicted in the Fig 8.1 and described in additinal detail by analysis of difference.
Univariate analyses were executed to further analyze interval difference scores. To justify the length of the washout period, we compared the DQ values at baseline with the measurements after washout of scopolamine, using a paired-samples t test. The mean change in DQ from baseline to washout value was estimated to be -1.60 which was a non-significant difference (t = -0,464; df (38); *p* =.32, 1 tailed). This finding minimizes the probability of a carryover effect from scopolamine treatment to BoNT, indicating that the length of washout after scopolamine application was sufficient.
Changes in DQ (expressed as differences), SD, and p values between baseline and the subsequent measurements are tabulated in Table 8.2. All DQ measurements showed a significant decrease (mean differences ranging: 15.5 to 21.7; $p \leq .05$, based on paired-samples t tests).
The greatest reduction was achieved 2 weeks after BoNT injections (BoNT-2: mean difference score 21.7; SD 18.3; *p* =.000). The DQ increased slightly after BoNT-2. At the end of the study, though, a significant reduction of drooling was still found, implying an ongoing effect.

Table 8.2: Mean differences between baseline and follow-up measurements

	DQ		VAS	
	Difference (SD)	**Significance#**	**Difference (SD)**	**Significance#**
Bl / scopolamine	17.7 (21.2)	0.000	-34.3 (30.9)	0.000
Bl / BoNT-2	21.7 (18.3)	0.000		
Bl / BoNT-4	16.1 (18.9)	0.000	- 30.1 (22.8)	0.000
Bl / BoNT-8	20.0 (20.5)	0.000	- 22.1 (23.9)	0.000
Bl / BoNT-16	15.5 (19.1)	0.000	- 20.5 (24.9)	0.000
Bl / BoNT-24	15.7 (16.4)	0.000	- 13.5 (25.7)	0.002

Bl = baseline; BoNT = Botulinum toxin; BoNT-X = interval in weeks after injections; DQ = drooling quotient; VAS = Visual Analog Scale.
#paired-samples t tests, one-sided *p*-value ≤.05

During additional analysis, scopolamine measurements were compared with the measurements after BoNT injections up to 24 weeks (Table 8.3).

Table 8.3: Mean differences between scopolamine and BoNT measurements

	DQ		VAS	
	Difference (SD)	**Significance#**	**Difference (SD)**	**Significance#**
Sc / BoNT-2	4.1 (16.5)	0.131		
Sc / BoNT-4	- 1.6 (19.2)	0.604	4.2 (31.3)	0.405
Sc / BoNT-8	2.4 (21.7)	0.502	12.2 (30.9)	0.018
Sc / BoNT-16	- 2.2 (21.8)	0.528	13.7 (32.9)	0.013
Sc / BoNT-24	- 2.1 (20.2)	0.529	20.7 (39.9)	0.002

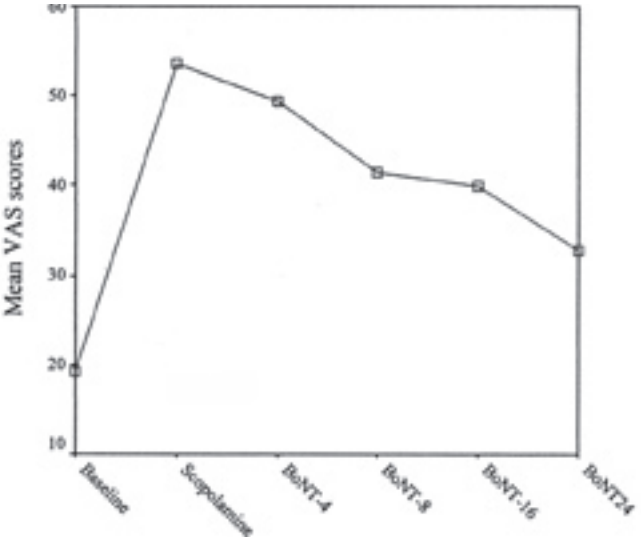
Sc = scopolamine; BoNT = Botulinum toxin; BoNT-X = interval in weeks after injections; DQ = drooling quotient;
#with paired samples t-tests, one-sided *p*-value ≤ 0.05

No significant differences were found (mean differences; -2.2 to 4.1; $p > 0.05$, based on paired-samples t tests). Analysis of "worst case scenario" data did not lead to different results comparing baseline with both treatments.
According to our definition of success to therapy, patients could be assigned as a responder if baseline DQ decreased by 50% or more during the interventions. Analysis of frequencies was done. During scopolamine, 53% of the patients were recognized as responders. Response rates to BoNT were as follows: BoNT-2, 64.1%; BoNT-4, 43.5%; BoNT-8, 53%; BoNT-16, 41%; and BoNT-24, 48.7%.

VAS

The analysis of the VAS showed an effect over time. With the VAS at each moment in time defined as the within-subjects variable, a MANOVA with a repeated measurements design was executed to evaluate the pattern of response during the trial (Hotelings trace: $F = 16.55$; df (5); $p = .000$). Fig 8.2 shows the course of the mean scores at the subsequent measurement moments.

Figure 8.2: Mean VAS in time



VAS = Visual analog scale; BoNT = Botulinum toxin;
BoNT-X = interval in weeks after injections

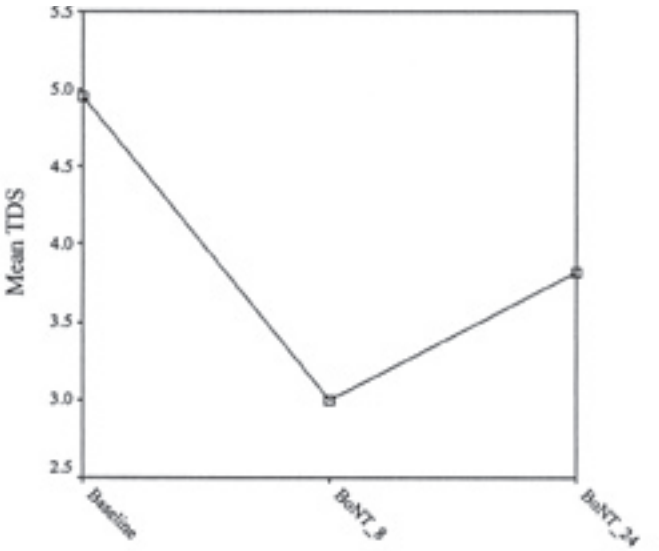
The degree of reported drooling by the parents declined substantially when baseline numbers (VAS: 19.3; SD: 13.4; range: 2-61) were compared with measurement during scopolamine application (VAS: 53.6; SD: 13.4; range: 0-96). Measurements scored by the parents after BoNT demonstrated good results with a maximum reduction at BoNT-4 (VAS: 49.3; SD: 24.5; range: 8-93). The VAS score at BoNT-4 was in the same range as during scopolamine application, revealing no significant difference (mean difference: 4.2; SD: 31.3; t -0,842; df = 38; p = .20, 1-tailed). Analyses of VAS difference scores were performed, using paired-samples t tests to compare baseline values with the results after therapy (Table 8.2). All differences were significant, indicating that parents reported diminished drooling throughout the study. In addition, scopolamine VAS scores were compared with all subsequent BoNT measurements (Table 8.3), using paired-samples t tests. No differences were found meaning that the outcomes of both therapies as reported by the parents were in the same range.

TDS

Patients had to score 3 or higher on the TDS to be included in the study. At start of the study 94.9% of the patients had a score of 5 with the remaining 5.1% having a score of 4. A success to therapy was defined as a 2-point improvement on the TDS (see

methods). The Wilcoxon signed-ranks test was used to analyze changes in TDS over time. Compared with baseline, a significant decrease was observed at BoNT-8 (Z = -4.8; p = .000, 1-tailed) and BoNT-24 (Z = -4.1; p = .000, 1-tailed). The TDS is an ordinal scale; as such, the outcome can only provide supportive evidence. To confirm the outcome, the TDS should show changes in the same direction as the VAS (Fig 8.3).
The curve shows that at baseline, all patients were severely drooling (mean: 4.9). Drooling diminished after BoNT injections. At BoNT-8, the mean score decreased to 3, indicating occasional drooling. At BoNT-24, the mean TDS score equaled 3.8.

Figure 8.3: Mean TDS in time



TDS = Teacher drooling scale; BoNT = Botulinum toxin; BoNT-X = interval in weeks after injections

The TDS was also used to define success to therapy (see Methods). An analysis of frequency of scores on the TDS was made to provide insight into parents' recognition of the BoNT therapy effect. Eight weeks following the BoNT injections, TDS scores were as follows: 1, 15.4%; 2, 28.2%; and 3, 17.9%. This indicates that 61.5 % of the patients were good responders according to our definition. 15.4 % of the children changed only slightly (score: 4). Twenty-three percent of the cases, representing 9 patients, did not show improvement compared to their initial score. Eight (20.5%) patients remained at score 5 and 1 (2.5%) patient at score 4. None of the parents reported an increase in drooling severity as a result of therapy.

None of the patients showed improvement between BoNT-8 and BoNT-24. TDS frequency scores at BoNT-24 were as follows: 1, 5.1%; 2, 15.4%; 3, 15.4%; 4, 20.5%; 5, 43.6%. At 24 weeks following BoNT injections, 35.9% of the parents still reported a good effect, whereas 43.6% of the children had returned to baseline value, among them the 20.5% who did not react to therapy at all.

Side effects

Parents scored the extent of side effects on a 4-point scale (0 = no side effect; 1 = mild, not every day/occurring sometimes; 2 = moderate, present every day; 3 = severe side effect, constantly present). Side effectsas a result of scopolamine became apparent within the first three days of administration, and several patients complained of >1 symptom. Adverse effects during application of scopolamine were reported in 82.2% of cases. Five (11.1%) patients had mild, 14 (31.1%) patients had moderate, and 18 (40%) patients had severe side effects.

Most often reported adverse effects were xerostomia (66.7%), restlessness (35.6%), somnolence (35.6%), blurred vision because of pupillary dilatation, and confusion (20%). Four out of the 6 dropouts from the study had to end their participation because of adverse effects to scopolamine. In all 4 cases, restlessness, apparent in their movement performance, and confusion were the main reasons to terminate scopolamine use. After BoNT injections, incidental side effects were reported. Two (5.1%) patients had a transient flu-like syndrome lasting for <2 days. Another 3 patients complained of mild difficulty with swallowing.

Discussion

This is the first controlled, clinical trial evaluating the treatment of drooling in children with CP by comparing the efficacy of 2 different anticholinergic agents: bilateral single-dose BoNT injections into the submandibular glands and transdermal scopolamine. A positive clinical effect from intra-glandular BoNT injections as well as scopolamine application was found. Scopolamine was expected to have a greater effect on drooling because of its systemic availability, influencing the submandibular glands, the sublingual glands, and the parotid glands apart form all minor glands within the mucosa of the oral cavity. As chosen during this trial, BoNT is injected only focally into the submandibular gland. Nevertheless, the short-term effect on drooling by intra-glandular BoNT injections was of the same magnitude as that of scopolamine. This outcome is compatible with the concept that the submandibular glands produce a large

part of resting saliva. In addition, it underlines that BoNT has a strong anticholinergic effect in the target glands.

The outcomes of clinically relevant parameters (DQ and VAS) were in accordance with each other, showing a reduction in drooling following both interventions. The parents' reports about their child's drooling at home (VAS scores) showed significant change. A similar positive effect was demonstrated in the reduction of DQ after BoNT injections up to 24 weeks, the end of the study. Response rates, as analyzed in the DQ data, were high. Of all patients, 53% responded during scopolamine, 64.1% responded 2 weeks after BoNT injections, and 53% responded 8 weeks after injections. After 24 weeks, 48.7% of the patients still responded to BoNT. Success to therapy was also defined as a 2-point decrease of the TDS as compared with baseline. Eight weeks after BoNT injections, 61.5% of the patients could be registered as responders according to the TDS approach. At the end of the study (BoNT-24), 35.9% of the patients were still responding to the BoNT injections.

The outcome of success to therapy as described with the DQ is based on an objective observation expressed on a numerical scale. The result of the TDS is a subjective expression on an ordinal scale. Still, the results of both observations on BoNT are congruent. Comparable outcomes on drooling in BoNT studies have been reported in observational studies[9;10].

Transdermally applied scopolamine and oral anticholinergic agents like glycopyrrolate and benztropine have been widely investigated in the treatment of drooling[8;15;27-34]. Lewis et al randomly assigned patients to a 2-weeks use of scopolamine patches and placebo patches using a cross-over design[31]. Success to therapy was recorded in 80% of patients. Blasco performed a prospective open-label study in which 90% of the patients had reduced drooling in response to glycopyrrolate, based on the subjective reports by parents[28]. Bachrach investigated the results of glycopyrrolate among 37 patients in a questionnaire based cohort study[27]. Parents were asked to describe the amount of drooling before medication had begun and while their child was taking the medication, using a five-point scale. A significant improvement was present in 95% of cases. Mier et al used increasing dosages of glycopyrrolate in a placebo-controlled clinical trial[32]. According to their definition of success to therapy, 81% of patients responded to the highest dosage. The abovementioned success rates all exceeded the 53% responders found in the present study. An explanation for this difference could be that the definitions of response (a 50% reduction or more of the DQ, in our study) used in the studies are not be interchangeable.

Disadvantages of systemic anticholinergic drugs are the many side effects. Severe side effects were observed in 40% of cases. Symptoms like xerostomia, restlessness, somnolence, blurred vision, and confusion were apparent in this study, necessitating ending the therapy in 7% of the participants. In this way, 4 of 6 dropouts were due to scopolamine. It was theorized that side effects are probably even underscored in this study population, taken into account the patients' inability to present their complaints clearly. Besides, scopolamine was applied for a relatively short period. Thus, continued use of scopolamine in a dosage large enough to treat severe drooling seems undesirable.

Side effects due to anticholinergic therapy are also described in other studies. Lewis et al (1994) reported two-third of his population to have pupillary dilatation and ~ 27% demonstrated pruritus or increased mouthing behavior as a reaction to scopolamine31. Applying glycopyrrolate (Blasco, 1996), 32.5% of the patients had adverse effects of which behavioral changes (13%) were specified in a percentage[28]. Mier et al reported that adverse effects were common, affecting 69% of the children taking glycopyrrolate[32]. The identified side effects ranged from 10 to 23%, comprising behavioral changes, facial flushing, nasal congestion, constipation, vomiting, diarrhea, dry mouth, urinary retention, and blurred vision. Seven of 36 participants withdrew from the study because of side effects. Although side effects seem to be common in relation to the use of anticholinergic drugs, the intensity and the occurrence of central effect may vary, depending on the drug of choice.

BoNT led to temporary complaints about swallowing in 2 cases. This was ascribed to local swelling in 1 patient. In another case moderate difficulty with swallowing developed after 1 week and remained for 10 days. It was theorized that this might have been the result of diffusion of BoNT into the surrounding muscles. Other authors explicitly noted that no side effect were seen following BoNT injections[23].

BoNT, when accidentally injected next to the salivary glands, will influence neural activity at the neuro-muscular junction as well. To avoid side effects and achieve optimal results, ultrasound guidance is strongly recommended[5;23;35;36]. Although easy to perform, BoNT injections are to some extend invasive. General anesthesia could be regarded as a disadvantage. In this respect it most be emphasized that other authors perform the procedure without anesthesia[23].

As chosen in our protocol, only the submandibular glands were treated. However, it must be realized that there may exist indications to treat the parotids as well, for example excessive drooling during eating and drinking.

To our knowledge, this is the first controlled clinical trial in the treatment of drooling, evaluating the effect of scopolamine application and intra-glandular BoNT injections into the submandibular glands. Both treatments significantly reduced drooling compared with baseline. The outcome of both therapies is in the same range and, no significant differences were found between DQ measurements during scopolamine and BoNT. A disadvantage in the treatment with scopolamine is the high percentage of observed adverse reactions, whereas BoNT injections need general anesthesia in children. The BoNT effect is temporary, although longer duration might be expected especially after recurrent treatment because of supposed hypotrophy of the glands after long denervation. Referring to the demands about the diagnosis and TDS, as stated in the inclusion criteria, the generalizability of this study is limited to comparable groups of patients. Further research is needed to investigate BoNT therapy in other groups and to compare it to other interventions to treat drooling, such as surgery. Considering the social burden to the affected children it is relevant to develop clinical guidelines to distinguish types and age groups of drooling patients in order to optimize the treatment modalities that are specifically effective.

In conclusion, during scopolamine application as well as after intra-glandular BoNT injections a clinically relevant reduction of drooling was achieved in children with CP, demonstrating maximum effect 2 to 8 weeks after injections. Analysis of the DQ demonstrated a response rate to scopolamine of 53% and of nearly 50% until 24 weeks post BoNT injections, the actual duration of this study. Additional research is warranted to optimize selection of patients in an effort to maximize the therapeutic effect.

Acknowledgements

This work was supported by a grant from the Johanna Kinder Fonds (Arnhem, the Netherlands), a fundraising consortium in the field of child rehabilitation.

We express our gratitude to Frank Joosten MD PhD and Lia van Die MD, radiologists, and Ricky van der Heijden, trial monitor, for their essential professional contribution to the study.

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Chapter 9

The treatment of posterior drooling by Botulinum toxin

Submitted for publication

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Abstract

Background: anterior drooling and posterior drooling are two distinguished phenomena. The latter refers to saliva that is spilled over the tongue through the faucial isthmus. Posterior drooling in children with cerebral palsy may lead to salivary aspiration and pneumonia. The objective of this study was to evaluate the effect of Botulinum toxin on posterior drooling.

Method: the mechanism of posterior drooling and the consequences are described and illustrated by the case report of a severely drooling 9-year old boy with cerebral palsy. He was treated by repeated bilateral intra-glandular Botulinum toxin injections in the submandibular glands. Salivary secretions were measured from all major salivary glands to obtain information about the flow rate from each oral region. In addition, the degree of drooling was assessed by an observational method, and by means of Visual Analog Scales that were completed by the parents. Video fluoroscopic swallow studies were done to evaluate the situation before and after treatment.

Results: the salivary flow rate from the injected glands was substantially reduced. Visible anterior drooling diminished substantially. From the clinical course after injections a reduction of posterior drooling became clear. Episodes of recurrent pneumonia, as were seen before treatment disappeared for 7 to 12 months.

Conclusion: Injections with Botulinum toxin may become to play an important role in the treatment of posterior drooling, although further research in a larger group of patients is needed.

Introduction

Impairment in swallowing can result in drooling, which has been reported in about 10 to 37.4% of cases of children with cerebral palsy (CP)[1;2]. These children often have a poor synchrony of lip closure, demonstrate an open bite, score lower on tests for oral sensation, and have a lower frequency of conscious swallowing[3-7].

The mechanism of drooling is explained by disturbances in the phases of normal swallowing: 1) the oral 'preparatory' phase, 2) the oral phase, 3) the pharyngeal phase, and 4) the esophageal phase. The preparatory and oral phases are completely voluntary, the pharyngeal phase has both voluntary and involuntary components and the esophageal phase is fully involuntary[8].

The oral preparatory phase is needed to form a bolus. The length depends on the composition and texture of the food. The oral preparatory phase becomes important when spoon-feeding starts, normally at four to six months of age. Lip closure is needed

to hold the bolus in the mouth and the soft palate is brought in a lowered position, to prevent the bolus from entering the pharynx before a swallow is initiated. The larynx and pharynx are at rest and there is an open airway enhancing nasal breathing. The onset of the oral phase starts with elevation of the tongue of which the anterior part contains the bolus. The tongue carries the bolus in posterior direction by peristaltic movements, making sequential contact with the hard and soft palates. On the average, the length of the oral phase is about 0.5 seconds. The voluntary control of swallowing ends when the bolus reaches the posterior pharyngeal wall and continues into the pharyngeal phase of swallowing. The initialization of the pharyngeal swallow reflex occurs when the bolus appears in the space between the soft palate and the tongue, or when the bolus accumulates in the valleculae. This results in elevation of the soft palate, which closes the nasal-pharynx. The larynx closes to protect the airway in combination with relaxation of the upper esophageal sphincter. The pharyngeal phase of swallowing continues automatically in the esophageal phase of swallowing.

Drooling is the unintentional loss of saliva from the mouth, known as anterior drooling[9;10]. However, anterior drooling has to be distinguished from posterior drooling which refers to saliva that is spilled over the tongue through the faucial isthmus. Under physiological conditions this initiates the pharyngeal phase of swallowing, during which the larynx closes to protect the airways followed by relaxation of the upper esophageal sphincter. Whenever the trigger to swallow is impaired or missing pooled saliva may lead to posterior drooling mostly apparent from an alarming congested breathing, coughing, gagging, vomiting, and at times aspiration into the trachea. Unrecognized and "silent" pneumonia can occur[11;12]. The risk of posterior drooling can be enhanced by the fact that many disabled children are taken care of in a supine position for a substantial part of the day.

A complex interaction exists between gastro esophageal reflux and salivary flow rate. In healthy subjects exposure of the distal esophagus to acid results in an immediate increase of saliva secretion. The possible function of this is that swallowed saliva plays a role in the defense of esophageal mucosa to acid-induced injuries. Reflux in children with CP causes stimulation of pH-sensitive receptors in the mucosa of the distal esophagus which activates the esophageal-salivary reflex leading to an increase of salivary flow rate with resultant drooling[13;14]. The same mechanism may also cause deterioration of posterior drooling. In addition, chronic gastro esophageal reflux itself is a well-known clinical entity causing chronic aspiration of gastro-intestinal contents[15-17]. Up to 60% of severely impaired children aspirate[18;19].

Botulinum neuro-toxin (BoNT) injections in the salivary glands in the treatment of anterior drooling demonstrate promising efficacy[20-24].

This case-report summarizes the results of repeated bilateral single-dose BoNT injections into the submandibular glands in a patient with CP with severe drooling, aspiration, and recurrent pneumonia. The primary treatment intention was to decrease salivary flow in an effort to reduce anterior as well as posterior drooling.

Patient and methods

The patient

A male (9 yr and 4 months of age; diagnosis CP; quadriplegic spastic athetosis; wheelchair dependent) was referred to our outpatient clinic because he constantly drooled in a manner that clothes, furniture, and objects became wet. He used to withdraw from peer activities because of his drooling.

Detailed characteristics of the patient are tabulated in table 9.1.

Table 9.1: Characteristics at entry of the study

Gender	Male
Age at entry of the study	9 years; 4 months
Birth	A term; vacuum extraction; Apgar: 4-4-5; Intra-cerebral bleeding
Diagnosis	Cerebral palsy; Quadriplegia; Epilepsy; Mental retardation
Movement disorder	Spastic/dyskinetic movement disorder; Ashworth score 4 (arms and legs)
Unsupported sit	Not possible
Head balance	Insufficient
Mobility	Wheelchair bound
Activity of daily living	Dependent
Feeding	Feeding and swallowing problems; Percutaneous gastro-stoma (at age 3 yr)
Oral motor performance	Hyper-tonicity
Hyper-reflex activity	Slow uncoordinated tongue movements; tongue trusting activities
Increased swallowing time	Hyper sensibility
Insufficient lip closure	Mal occlusion
Speech	Anarthria; use of 'my voice' computer aided communication
Drooling	Profuse Anterior and Posterior Drooling; TDS score of 5
General health	Chronic distal esophagitis; gastro-esophageal reflux; Recurrent pneumonia

In the 2 years prior to consultation episodes of pneumonia had occurred averagely 7 times a year. He had gastro-esophageal reflux and was mainly fad by a percutaneous endoscopic gastrostomy (PEG). Stasis of saliva in the oral cavity and hypopharynx was always present. Congested breathing resulted in restless sleep during which he choked on his own saliva. He used an anticholinergic drug to reduce the discomfort of drooling.

Assessments

The oral anatomy, sensitivity, reflex activity, and oral-motor skills were assessed (Table 9.1).

To measure salivary flow rate the 'swab method' was used during which absorbent dental cotton rolls (Salivette®: Sarstedt B.V, Etten-Leur, The Netherlands) were placed directly at the orifices of the larger glands for a 5-minute period. The salivary flow rate for each separate salivary gland was calculated by the formula:

Salivary flow rate [mL/min] = (weight increase of dental rolls / time of collection). The assessments were conducted by the same speech pathologist, always in the morning following 1 hour of starvation. The procedure was repeated 30 minutes later. The mean of the two measurements was used as the result for the study.

Because of the close anatomical relation between the sublingual and submandibular glands, separate flow rates could not be obtained. The compound salivary flow from these two glands is referred to as submandibular flow (SubFl).

The drooling quotient, visual analogue scales, and the Teacher Drooling Scale (TDS) were used to assess the degree of drooling[25].

The TDS rates anterior drooling on a 5-point scale. A score 5 indicates 'constantly wet and saliva leaking on clothes and furniture', 3 means 'occasionally drooling', and 1 indicates 'no drooling'.

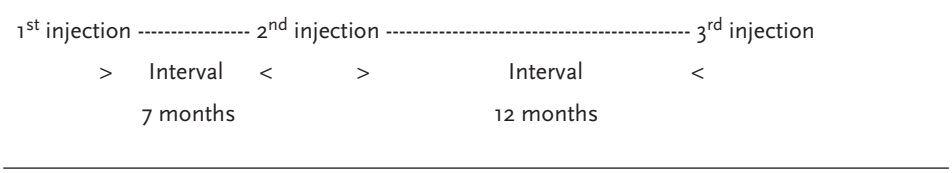
The drooling quotient (DQ), an observational method, was scored according to its original design during two periods of 10 minutes separated by a 60-minute break. An episode of drooling was defined as new saliva present on the lip margin or leaving the chin. Every 15 seconds (40 observations in 10 minutes) the presence or absence of drooling was assessed. Evaluation took place at least one hour after a meal while awake and sitting erect. The DQ was expressed as a percentage estimated from the ratio of observed drooling episodes and the total number of observations (DQ [%] = 100 X number of drooling episodes/40)[26]. The mean of both observations was used for analysis providing an outcome on a numerical scale.

Visual analog scales of exactly 10 cm without visible subdivisions were presented to the parents. The average degree of drooling severity had to be indicated concerning the two weeks before assessment. Scoring, measured with a ruler in mm. resulted in a numerical outcome.

The patient was indicated for bilateral Botulinum toxin injections in the submandibular glands. Only the submandibular glands were injected. It is generally accepted that these glands produce 60 - 70% of secreted resting saliva, when the individual is neither eats nor drinks. The parotids respond explicitly during eating and drinking, producing much serous saliva, with which we did not want to interfere.

The patient was followed in our clinic for several years and repeatedly received BoNT injections (Fig. 9.1).

Figure 9.1: Scheme of BoNT injections



Two weeks before the third injection and 4 weeks after this intervention Video fluoroscopic swallow studies (VFSS) were performed to assess the efficacy of swallowing.

Intervention

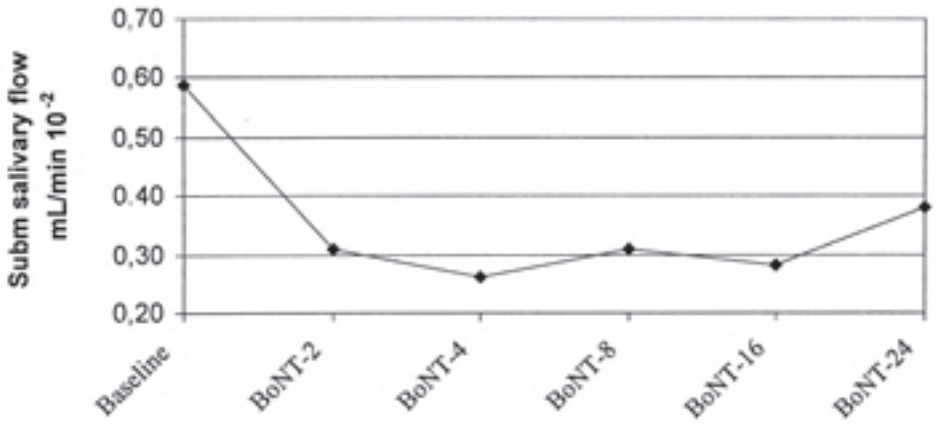
Under general anesthesia a single dose of 50 Units Botulinum toxin (Botox®: Allergan, Nieuwegein, The Netherlands) was injected bilaterally in the submandibular glands, using a 25 G needle (Spinocan®) and a 1 ml syringe. The total dosage was divided between the left and right gland. On injection, each dose was fractionated and divided over minimally three sites in the gland. To locate the glands, ultrasound guidance was performed using a system (SAL 250: Toshiba medical systems cooperation, Tokyo, Japan) equipped with a 7.5-MHz transducer.

The patient returned for follow-up measurements (Flow, DQ, VAS) at 2, 8, 16, and 24 weeks after the 1st BoNT injection and at 4, 8, 18, and 28 weeks after the 2nd injection. In addition, parents filled out extended questionnaires concerning items that could possibly be influenced by a change in salivary flow. Parents were also asked to register side effects of the BoNT injections in a diary.

Results

The first BoNT treatment was given at the age of 9 years and 6 months. In the months following injection the flow from the submandibular gland, as investigated by the 'swab method' decreased (Figure 9.1, Table 9.2).

Figure 9.2: Submandibular salivary flow rate before and after 1st BoNT injections



Subm=submandibular; BoNT-x=time interval in wks after BoNT injections

Table 9.2: Assessment of salivary flow rate and drooling before and after treatment

	Base I	$B_1$2	$B_1$8	$B_1$16	$B_1$24	Base II	$B_2$4	$B_2$8	$B_2$18	$B_2$28
SubFL	0.59	0.31	0.31	0.28	0.38	0.38	0.11	0.22	0.30	0.28
DQ	46	6	4	2.5	7.25	24	7.5	12.5	16	7

B=Botulinum neuro-toxin; B1x=time interval in weeks after first BoNT injections; B2x= time interval in weeks after second BoNT injections; SubFL=submandibular salivary flow rate; DQ=drooling quotient

The TDS scored 5 at baseline. Eight weeks after the 1st injections TDS decreased to 2, indicating 'sometimes drooling'. In accordance with this the DQ was reduced by 91.3% (from 46 to 4). The outcome of the VAS assessments showed a similar trend: according to the parents' opinion drooling was severe at baseline (VAS: 13) whereas it improved substantially 8 weeks after BoNT injections to mild drooling (VAS: 78). Approximately 6 months after the BoNT injections (control visit 24 weeks) parents reported that, to their opinion, drooling had started to increase (VAS: 34). The SubFL and DQ had increased slightly although a substantial difference still existed compared to baseline

(Table 9.2). Based on the registrations of SubFL, DQ and VAS a good impression was obtained about anterior drooling and the results after BoNT administration. In addition, it became clear that his posterior drooling as was present before the BoNT injections, improved. Two weeks after treatment parents reported his breathing to be improved because of less stasis of saliva in the oral cavity. During the entire control period he slept better, his condition improved, and he had no pneumonia. Although the controls of anterior drooling remained fairly good, parents reported congested breathing again after 7 months, which had been absent after BoNT treatment and for which no objective test or observational study, existed. Based on the clinical picture, suggesting the recurrence of posterior drooling, a second BoNT treatment was executed. The results of the follow-up measurements are presented in Table 9.2.

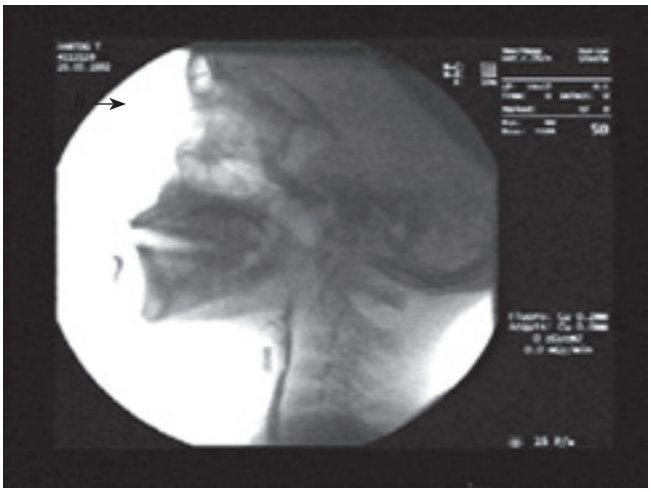
The symptoms of posterior drooling disappeared again after the 2nd injection and the pulmonary condition improved. During an outpatient visit, 10 months after the second treatment, pneumonia was reported. A third BoNT treatment was executed 12 months after the second injection.

VFSS's were done before and after the third injection in order to visualize the probable false route of saliva into the trachea and to gain better insight in the mechanism of swallowing.

The first VFSS was made some weeks before the 3rd BoNT injection when he was recovering from an episode of pneumonia. To conduct the study the patient received 3 mL thickened liquids (barium contrast). On analysis of the videos, the oral stage of swallowing showed poor and insufficient bolus formation. The tongue demonstrated inadequate peristaltic movements with limited transport of the bolus. The onset of the pharyngeal phase of swallowing was delayed and pooling occurred in the valleculae and pyriform sinuses. Following 3 attempts to swallow, the material was partially spelled over into the trachea (Figure 9.3).

Residual contrast medium was seen after the first swallowing actions and extended efforts were needed to clear the pharynx. There was no immediate cough or gag response to the aspiration which resulted in silent aspiration. The second VFSS was taken 12 weeks after the 3rd BoNT injection. His tongue movements were stronger and he showed no refusal to swallow. In contrast to the first study, the onset of the pharyngeal phase was not delayed. Pooling in the valleculae still occurred but was followed by an efficient swallow act, during which no aspiration was observed and less residual contrast medium was seen.

Figure 9.3: Video fluoroscopic swallow study prior to 3rd BoNT injection



#: Aspirated liquid.

Discussion

Our patient was repeatedly treated with BoNT injections bilaterally in the submandibular glands because of posterior as well as anterior drooling. With intervals of respectively 7 and 12 months he was treated three times with a total of 50 U Botox. The technique required ultrasound guidance and anesthesia for safe injections[27]. From the pharmacological profile of BoNT intra-glandular injections are expected to give an anticholinergic effect because it blocks the secretion of acetylcholine at the terminal nerve endings.

The results showed a marked decrease in submandibular salivary flow following the first injection (Figure 9.2) as well as a reduction in drooling (Table 9.2). The change in anterior drooling could be evaluated by investigation of the TDS, DQ and VAS scores. Posterior drooling was evaluated indirectly by a change of clinical symptoms like congested breathing, swallowing difficulties, and aspiration with associated pneumonia.

A recurrence of the salivary secretion from the submandibular glands was foreseeable since Botulinum toxin has a temporary effect. However, a striking finding was the longer time interval of the results after the second BoNT injection. It is hypothesized that hypotrophy of the injected salivary glands may arise due to long lasting denervation by BoNT.

Parents reported an improvement in eating after the first injections. From the

questionnaires it was concluded that 'fear to swallow' decreased, oral intake increased, and he gained more body weight. It was concluded that the diminished salivary flow rate caused less episodes of aspiration in particular during the night. The patient trusted himself more to swallow. In addition, there might have been less congestion of saliva at the faucial isthmus resulting in a decrease of defensive coughing relieving pharyngeal irritation. The vicious circle of irritation, with avoidance or refusal to swallow tended to return when the salivary flow from the submandibular glands increased again. Based on this experience video fluoroscopic swallowing studies were executed before and some weeks after the third BoNT injection. The patient had a bad condition during the first assessment and clearly demonstrated aspiration. The results of this study supported the parents' conviction that swallowing and deglutition were negatively influenced during episodes of diminished general health, e.g. during recurrent pneumonia. It was registered that the episodes of pneumonia decrease impressively after BoNT injections and, along with this, his physical condition improved. The conditions resulted in less irritation and pain during deglutition, a better swallowing mechanism, and the disappearance of aspiration. The VTSS 12 weeks after treatment showed an efficient swallow act without aspiration.

In conclusion: Posterior drooling in children with cerebral palsy can play an important role in the clinical picture as it can lead to (silent) aspiration. In the case we described in this article, BoNT injections in the submandibular glands resulted in a substantial reduction of submandibular salivary flow rate. From the clinical course after injections a reduction of posterior drooling was clear with the absence of recurrent pneumonia as the most important finding.

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Chapter 10

Quality of life in cerebral palsy: the evaluation before and after treatment of drooling

Submitted for publication

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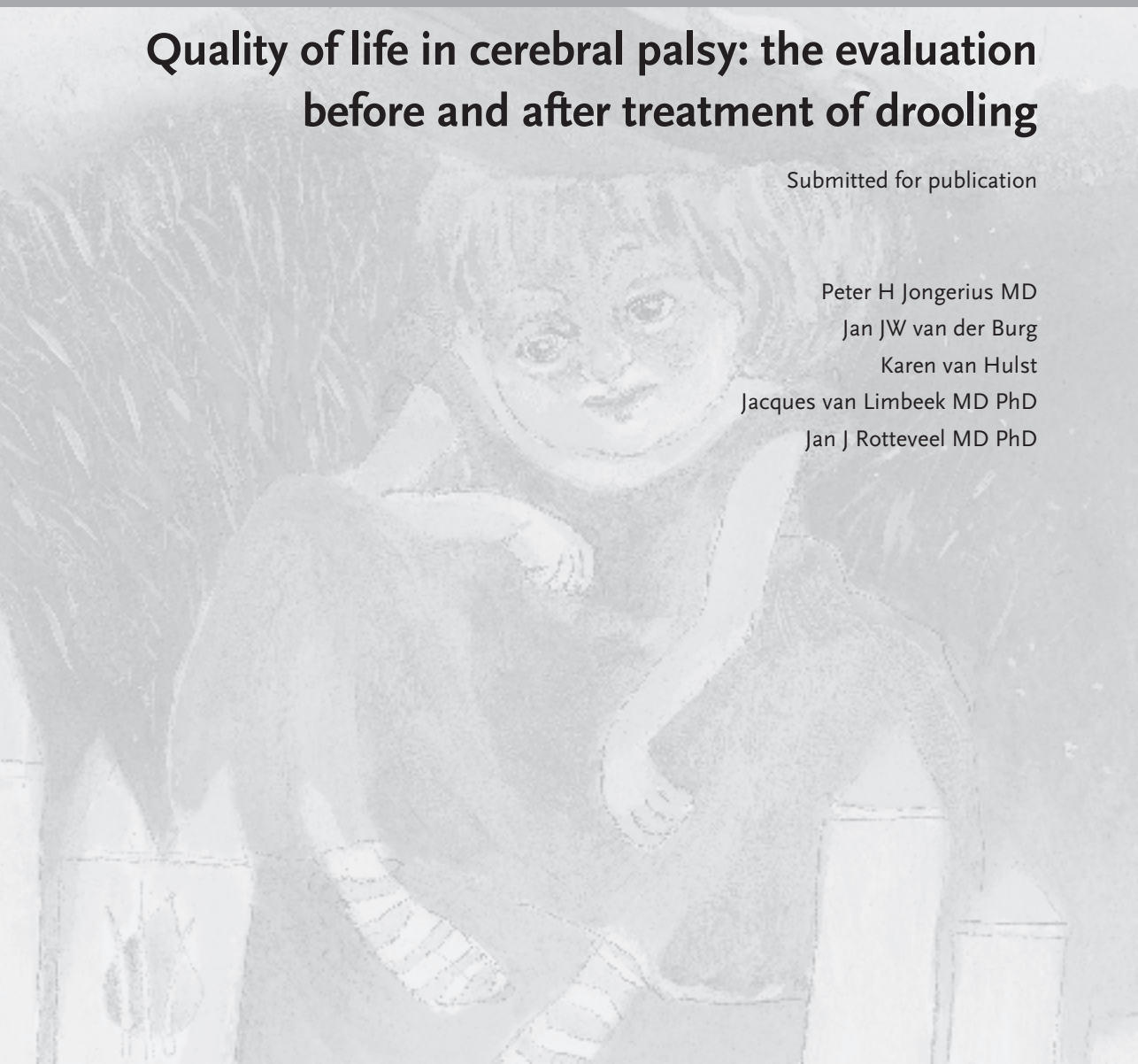


Abstract

Aim: to investigated the effect of treatment of drooling on Quality of Life. Methods: a questionnaire was developed containing items that were recognized as representative for Quality of life of drooling children and their families. Parents were asked to fill in the lists. Forty-five severely drooling children (mean age 9 years and 5 months, SD 3.7, 28 male and 17 female) were monitored before and after receiving medication to reduce the salivary flow.

Results: Anticholinergic agents effectively reduced salivary flow. Drooling diminished substantially, which was accompanied by a significant reduction in care-taking actions, making daily care less demanding. The number of damages to communication devices and computers decreased. Conclusion: In addition to the evaluation of primary variables such as the salivary flow rate, investigation of items of Quality of Life provides useful information about the outcome of drooling treatment, which can also be applied to surgical procedures.

Introduction

Drooling in children with cerebral palsy (CP) is primarily due to oral motor dysfunction resulting in inefficient and infrequent swallowing and poor lip closure[1;2]. It is a significant problem in 10-37,5% of patients with CP [3;4]. The evaluation of the effects of interventions is mostly directed to the salivary flow. However, during some studies parents also answered open-end questions concerning the severity of drooling to determine the outcome of an intervention[5-7]. After reviewing these studies, it was concluded that Quality of Life (QoL) is only roughly investigated in relation to drooling.

QoL research employs questionnaires that are either generic (e.g. the Child Health Questionnaire)[8] or condition specific (e.g. the questionnaires for children with cancer, asthma, etc). QoL assessment in children with CP is relatively recent[9-11]. So far, no validated questionnaires are available addressing specific problems such as drooling in children with CP.

An open-label controlled clinical trial during which patients were treated subsequently with scopolamine and Botulinum toxin (BoNT) has been conducted at the University of Nijmegen. A positive effect on salivary flow rate was seen for both anticholinergic agents (accepted for publication: Neurology/June 2004). The reduction in salivary flow rate was strongly related to a significant reduction in drooling (accepted for publication: Pediatrics/March 2004).

The objective of this study was to evaluate changes in aspects of QoL as a result of drooling treatment. The impact of drooling on daily life was investigated before and

after treatment, which was made operational by questionnaires, especially developed for this study, containing items of daily situations and daily care recognized as relevant aspects of QoL.

Method

Patients

Forty-five severely drooling patients with the diagnosis CP, recruited from the outpatient clinic, were included in a controlled, clinical trial evaluating the effect of intraglandular BoNT (Botox®, Allergan, Nieuwegein, the Netherlands) injections into the submandibular glands on drooling compared with the effect of application of transdermal scopolamine patches. Inclusion criteria comprised: boys and girls; pre-school and school age; diagnosis of CP; a score of 3 or higher on the Teacher Drooling Scale (Table 4.1). The latter comprises a 5-point scale to score the degree of drooling: 1) 'No drooling', 3) 'Occasional drooling on and off all day', 5) 'Constant drooling, always wet'.

All drugs used were carefully evaluated to assess their influence on saliva secretion. Continuous use of anticholinergic drugs or benzodiazepines was not allowed. In particular clonazepam was a reason for exclusion. Throughout the study no change in medication was allowed. Medication to treat drooling had to be stopped at least three months before participation. All possible adverse effects and risks related to the study were explained to the parents and written informed consent was obtained. The Hospital's Human Research Committee approved the study.

Data collection

Parents may serve as excellent proxy for their children when assessing health related QoL[12]. For this study, a detailed questionnaire, to be filled in by the parents, was developed to evaluate the impact of drooling on items of daily life. The prerequisite for the items was that an expert team, consisting of a speech therapist, clinical pediatric psychologist and physician in rehabilitation medicine, reached consensus that the selected items reflected relevant aspects of QoL. The parents of three children who participated in a pilot study were invited to comment on the preliminary version of the questionnaire, which resulted in some adjustments[13]. The questionnaire contained open-end as well as multiple-choice questions. In addition, parents scored several visual analogue scales (VAS) to give their opinion about some statements about drooling and its consequences.

The data from two sections of the questionnaire (see appendix) are presented: the 1st

containing questions about drooling severity assessed for specific daily situations or activities (each item had a score range from 1 indicating 'no drooling' to 9 indicating 'very severe drooling', the 2nd section containing open-end and multiple-choice questions about practical consequences for daily care that were supposed to be influenced by drooling itself or possibly could improve after treatment of drooling.
Parents received detailed spoken instruction how to score, which was also written in the introduction of the questionnaire. The questions concerned the situation of the two weeks before assessment. Assessments were made at baseline, during the use of scopolamine, and 4, 8, 16, and 24 weeks following BoNT injections.

Data handling
Missing values occurred because of incomplete response, non-interpretable answers, or unanswered questions. Prior to data analysis, missing values were imputed by using the method of 'carrying the last observation forward' (CLOF), meaning that missing data after scopolamine and BoNT injections were replaced by the last available score on the same item. Missing values at baseline were estimated by imputing the mean (in case of a numerical score) or the median (in case of a ordinal score) of all participating children.

Statistical Analysis
From all investigated items, we identified those situations for which the parents of at least 50% of the children scored 'severe drooling' at baseline (Table 10.1). To evaluate the severity of drooling in these situations over time, we used an analysis of variance technique for repeated measurements with the scores of the degree of drooling as the dependent variable.

Table 10.1: Patients scoring 7, 8 or 9 on a 9-point drooling severity scale for specific items

Condition	Ns	Nd	(%Nd)	Condition	Ns	Nd	(%Nd)
Level of activity				**Body position**			
demanding activity	29	33	(88)	unsupported sit	26	33	(79)
strenuous activity	28	32	(88)	prone position	25	33	(76)
intensive movement	24	25	(96)	supported sit	24	35	(69)
relaxed, watching TV	21	33	(64)	supine position	6	30	(20)
walking	11	17	(65)				
sleeping	4	28	(14)				
Sensorimotor factors				**Mood, physical condition**			
eating	20	34	(59)	enthusiastic	27	33	(82)
drinking	19	26	(73)	tired	25	32	(78)
certain tastes or foodstuffs	16	21	(76)	sick	19	29	(66)
after brushing teeth	13	29	(45)	cries	18	27	(67)
teething	12	15	(80)				
talking	9	17	(53)				
smell of food	9	19	(47)				
				Medical factors			
				broncho/pulm. reactions	14	16	(88)
				using medication	9	18	(50)
				after taking medication	8	17	(47)

Ns = number of severely drooling children,
Nd = number of drooling children,
%Nd = percentage of Nd-children drooling severely

In order to evaluate the effect size for these items Cohen's d was calculated by comparing the mean baseline score of all patients to the mean at follow-up. The effect size was defined 'large' in cases Cohen's d exceeded 0.8[14].

To evaluate changes in daily parental care, analysis of variance techniques for repeated measurements were used for each individual item and Cohen's d was estimated. Non-parametric tests were conducted on appropriate items, such as damage to clothing, toys, books, furniture, communication aids, electric devices, or computers.

A *p*-value equal to or of less than 0.05 was demanded for all tests. Because of multiple testing in tests of within-subjects effects, we used a Bonferroni correction (i.e. 0.05/ number of tests).

Results

Forty-five children were included ranging in age from 3 to 16 years, mean 9 years and 5 months, SD 3.7, 28 male and 17 female. Eight children were ambulant without aid, 37 children were wheelchair bound. Twenty-two children could not talk. None of the children attended mainstream schools: 29 attended a special education school, and 14 attended a daycare center for mentally handicapped children. Thirty-four children were retarded with a developmental age below six years as determined by psychological investigation. No child had to be excluded because of use of medication. Of all patients, 21 did not use medication, four patients incidentally used benzodiazepines to treat epileptic seizures, and two patients stopped medication that was given to treat drooling. None of the subjects had Botulinum toxin before.

A response-rate of 85% was achieved (199 out of the initial 234 lists were returned).

The outcome of baseline investigations

Table 10.1 presents the specific conditions for which severe drooling, was scored. Each cluster of items starts with the condition most frequently scored. Because some of the items were not applicable for an individual child the actual percentage of involved children are given.

In particular, severe drooling occurred during strenuous activities that demand a higher level of concentration, such as during walking and sports. On the other hand severe drooling was observed in situations during which insufficient attention was paid to the need to swallow, such as watching television.

Severe drooling influenced the care and attention given to the child. For example, 18 children were told to swallow averagely 25 times per day, and 26 children had their mouth and chin wiped averagely 73 times per day. Thirty-one wore bibs or a shawl, which had to be replaced seven times a day. In thirty-one children clothes were redressed every day of which 16 repeatedly. Five children wore terry cloth wristbands. Parents ran nine (range 2-25) loads of wash averagely per week. They also reported damage to clothing (77%), toys (44%), books (44%) and furniture (46%) that was ascribed to drooling. In addition, communication aids (n = 9), electronic communication devices (n = 8), computers (n = 10), and audio equipment (n = 6) were damaged. Forty-one percent of the parents reported curtailing the child's play with objects that could be damaged.

The outcome of repeated measure analyses: daily situations

A MANOVA with a repeated measurements design was executed for those items on which 50% of the sample, representing at least 19 children, demonstrated severe baseline drooling. For nearly all situations a significant change was recorded after intervention (Table 10.2).

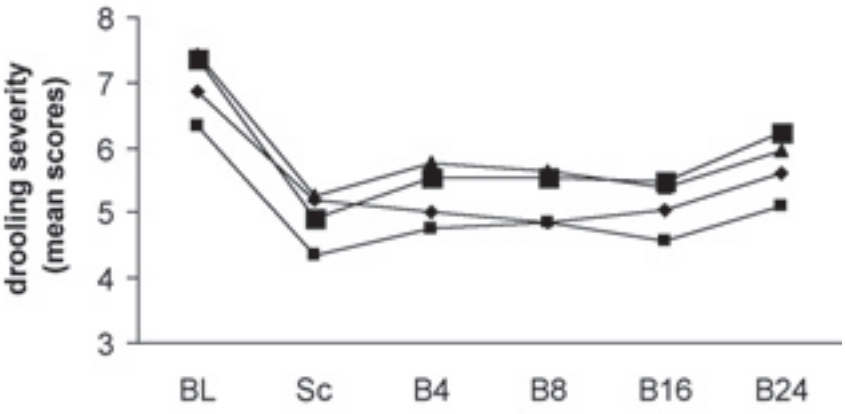
Table 10.2: Drooling in daily situations

Situation	Multivariate Tests HT2 (*p*)	Tests of Within-Subjects Effects F (df1, df2)	*p**	Effect-size: Cohen's d				
				Sc	B4	B8	B16	B24
Concentrated activity	1.65 (0.002)	5.4 (5, 110)	< 0.001	5.530	4.009	4.880	4.331	3.254
Strenuous activity	1.48 (0.002)	7.2 (5, 115)	< 0.001	6.580	4.491	5.532	4.848	3.235
Intensive movement (sports)	1.40 (0.056)	4,5 (5, 75)	0.001	4.530	3.785	4.535	4.755	3.437
Relaxed, watching TV	1,23 (0.008)	6,4 (5, 110)	< 0.001	4.350	3.846	3.939	4.623	2.287
Eating	2.21 (<0.000)	6.1 (5, 120)	< 0.001	4.647	3.675	3.728	4.290	2.441
Drinking	1.57 (0.009)	3.4 (5, 95)	0.007	2.956	2.460	3.099	2.404	1.475
Unsupported sit	1.56 (0.001)	6.7 (5, 120)	< 0.001	5.053	5.106	5.690	5.246	3.613
Prone position	2.82 (<0.001)	6.9 (5, 110)	< 0.001	4.648	5.103	4.548	4.330	2.004
Supported sit	1.86 (<0.001)	8.2 (5, 145)	< 0.001	6.472	5.555	6.087	5.613	4.489
Is enthusiastic	1.13 (0.009)	6.2 (5, 115)	< 0.001	6.029	4.397	4.763	4.058	2.684
Is tired	0.91 (0.046)	6.2 (5, 100)	< 0.001	4.350	4.191	3.994	4.191	2.218
Is sick	1.91 (0.248)	0.8 (5, 45)	0.561	-0.339	0.434	0.761	1.449	-0.443

multivariate tests with repeated measurements as factor (Hotelling's Trace (HT^2)),
tests of within-subjects effects (F-values (degrees of freedom) and *p*-value) and effect size Cohen's d comparing mean baseline scores to mean scores during Scopolamine treatment (Sc) and 4, 8, 16 and 24 weeks after BoNT injection (B4, B8, B16 and B24).
*Significance is reached when $p<0.004$

However, multivariate tests did not reach significance for the items 'intensive movement' (Hotelling's trace = 1.40; $p = 0.056$) or 'is sick' (Hotelling's trace=1.91; $p=0.248$). In all other daily situations, drooling severity decreased significantly during scopolamine application and 4, 8, 16, and 24 weeks after BoNT injection (Fig 10.1).

Figure 10.1: Mean drooling severity scores in specific situations



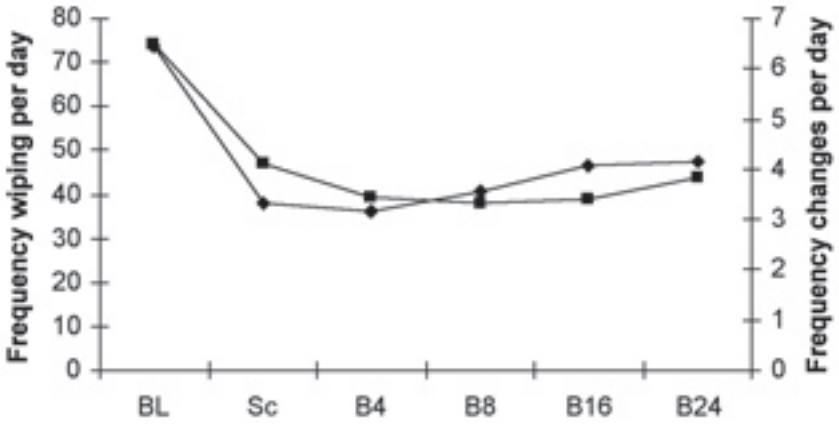
Drooling severity scores at baseline (BL), scopolamine treatment (Sc), and 4, 8, 16 and 24 weeks after BoNT injection (B4, B8, B16 and B24). Specific situation: unsupported sit (♦), eating (■), concentrated activity (▲), enthusiastic (x).

Except for 'is sick', Cohen's d exceeded 0.8 in all comparisons, indicating that the effect size was large throughout (Table 10.2).

The outcome of repeated measure analyses: practical consequences

Measures (provision of bibs, shawls, terry cloth wristbands, plasticized toys or books) taken to minimize the practical consequences of drooling were analyzed. A MANOVA with a repeated measurement design did not show significant changes in the number of the different measures. This also applies to the frequencies of urging the child to swallow (Hotelling's trace = .23; p = 0.289), changing shirts or sweaters (Hotelling's trace = .34; p=0.094), changing pants (Hotelling's trace= .12; p=0.620), and the number of washes per week (Hotelling's trace= .06; p=0.881). A significant decrease, however, was demonstrated in the frequencies of wiping the child's mouth and chin during the day (Fig. 10.2).

Figure 10.2: Mean frequency of specific actions



Frequency of specific actions at baseline (BL), Scopolamine treatment (Sc), and 4, 8, 16 and 24 weeks after BoNT injection (B4, B8, B16 and B24). Frequencies of: wiping the child's mouth and chin (■), mean frequency of changing bibs or shawls (♦)

Both, the multivariate tests (Hotelling's trace= .53; p=0.033) and the tests of within-subject effects (F=6.7; df=5,155; p<0.001) were significant and Cohen's d ranged from 2.350 to 3.463 comparing the mean baseline scores to the mean scores during Scopolamine or 4, 8, 16 and 24 weeks after BoNT injection. Frequencies of changes of bibs or shawls also decreased significantly (Fig. 2). Again, multivariate tests (Hotelling's trace= .79; p=0.002) and tests of within-subject effects (F=7.6; df=5,175; p<0.001) were significant and Cohen's d ranged from 2.459 to 3.683.

Parents reported no significant changes in the damage to cloths, toys, books or furniture as a result to therapy. However, a continuous decrease existed, from baseline up to 24 weeks after BoNT injection, in the damage to communication aids, electric devices, or computers (Chi-square=13,11; df=5; p=0.022).

Discussion

The daily care for drooling children is demanding and has practical consequences. In this study, a detailed questionnaire was developed to document the impact of drooling on Quality of Life of the children and their parents. A significant decrease of drooling in specific daily situations was demonstrated after salivary flow rate reduction by anticholinergic medication (scopolamine or BoNT injection). This was accompanied by a decrease in the frequency of wiping the child's mouth and chin and the frequency of changes of bibs or shawls, making daily care less demanding. Additionally, a decrease

of damage to communication aids, electric devices or computers was demonstrated. No significant change occurred for the items: 'sick', 'the frequency of changing clothes', or 'the number of washes per week'. Because sickness is not a daily recurring condition and parents were only asked to score over the two weeks prior to assessment, there seemed to be a lack of data for proper testing.

Frequencies of changing clothes probably did not change because there might have been other reasons than drooling to change clothes, for which we did not score. This could also explain why there was no change found in number of washes. Bibs or shawls are effective to prevent clothes from getting dirty even in the presence of small amount of saliva. This might be the reason why they were not entirely omitted, even in cases drooling practically disappeared.

This study proved that a reduction in salivary flow has significant and relevant effects on aspects of QoL. We recommend that all interventions to treat drooling (surgery, medication, behavior therapy, etc.) be evaluated not only on salivary flow rate, but also on items as are described in the questionnaire.

Acknowledgements: This work was supported by a grant from the 'Johanna KinderFonds': a fund raising organization for child rehabilitation in The Netherlands. The authors would like to gratefully thank Ricky van der Heijden, secretary, for her professional support to the study.

Appendix

Questionnaire Section 1

1. Mark in the first column all relevant conditions in which your child is drooling and if so, indicate for each condition the degree of drooling in the last two weeks prior to this investigation.

Condition	**Degree of drooling**				
supported sit	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
unsupported sit	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
prone position	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
supine position	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
walking	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
intensive movement (sports)	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
is sick	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
is tired	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
eating	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
smell of food	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
certain tastes or foodstuffs	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
drinking	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
talking	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
sleeping	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
concentrated activity	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
relaxed, watching TV	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
strenuous activity	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
is enthusiastic	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
swallowing medication	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
after swallowing medication	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
after brushing teeth	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
cries	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)
allergic reactions in bronchopulmonary tract	No (1)	Mild (3)	Moderate (5)	Severe (7)	Very severe (9)

Questionnaire Section 2

Daily care for drooling children takes extra attention and activities. Please answer the next questions as exactly as you can for the last two weeks prior to this investigation.

2. What measures do you take because of drooling?
   a. Child is wearing bib
   b. Child is wearing shawl
   c. Child is wearing terry cloth wristbands
   d. Child gets washable toys
   e. Books are plasticized
   f. Other measures,.....
3. How often his/her mouth or chin is wiped dry? ... times per hour or ... times per day
4. How often he/she is told to swallow? ... times per hour or ... times per day
5. How often his/her bib or shawl is replaced? ... times per day
6. How often his/her clothes are changed? ... times per day
7. How many loads of wash do you have? ... loads of wash per week
8. Has there been damage to:
   a. clothes yes / no
   b. toys yes / no
   c. books yes / no
   d. furniture yes / no
   e. communication aids yes / no / not relevant
   f. electronic communication devices yes / no / not relevant
   g. computer yes / no / not relevant
   h. audio equipment yes / no / not relevant

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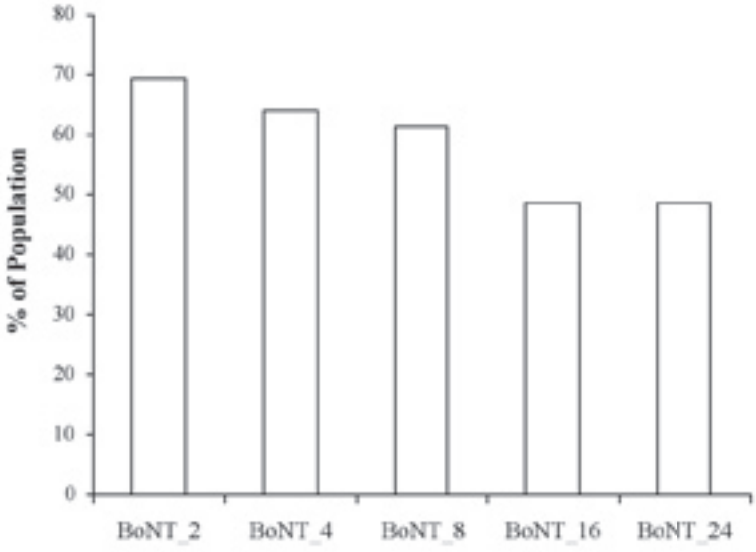
Chapter 11

General Discussion

This study offered new scientific information to the treatment options of drooling in children with various forms of cerebral palsy. The effect of intra-glandular BoNT injections was compared to an established treatment, for which the anticholinergic drug scopolamine was chosen. It was demonstrated that Botulinum toxin type-A (BoNT), injected into the salivary glands, reduces the salivary flow from these glands substantially in the majority of patients (Fig 7.2, Table 7.2). Compared to baseline, the control measurements of the primary outcome variables (the salivary flow rate and the drooling quotient) showed differences that were significant for at least 6 months following BoNT injections. We were able to measure 41% of the patients up to 40 week after the BoNT injections. The mean salivary flow from the injected submandibular glands was still in the same range as the mean of the whole population at 24 weeks. The same was true for the 21% of the patients that were measured 48 weeks after the injections. Although the number of patients after 24 weeks of follow up was to low to execute proper statistical analysis, the trend of the depicted curve is promising (Fig 11.1).

Figure 11.1: Response rate for salivary flow reduction (% of population)



BoNT_X: Measurements at subsequent moments (wks) following BoNT injections.

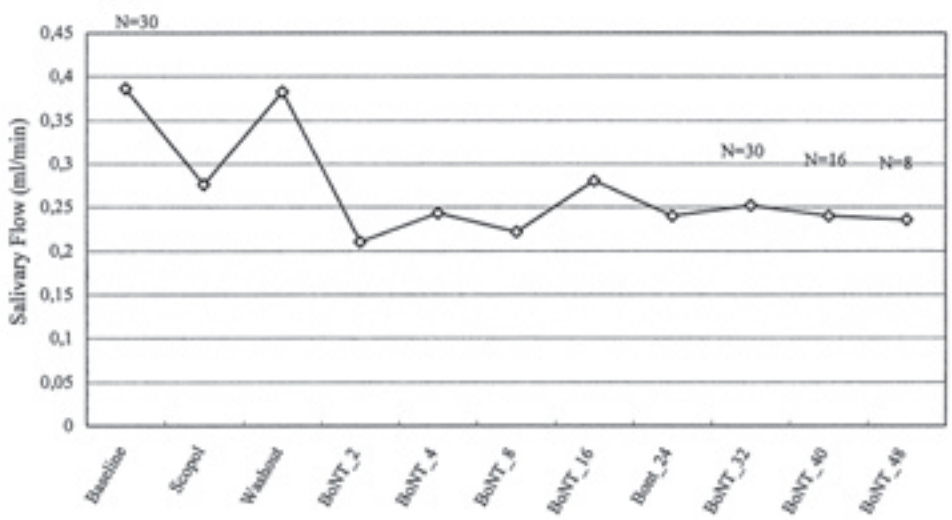
The BoNT effect is mediated by the autonomous nervous system. BoNT was already known to have an explicit effect on the parasympathetic part of the nervous system. In the treatment of hyperhidrosis, BoNT diminishes the secretion of sweat glands at least

for 9 months and many patients benefit for more than a year. This long lasting effect is strikingly different from the effect seen in the peripheral nerves of the motor system, which is about three to four months.
In this study the reduction in salivary flow was related to a significant decrease in drooling throughout the duration of the study (Fig. 8.1 and Table 8.2). The response to therapy was high for this new indication. In conclusion: intra-glandular BoNT injections are an effective way to treat drooling in multiple handicapped children with cerebral palsy.

11.1 The duration of the effect

In this study 60 to 70% of the patients demonstrated "success to therapy" with sufficient reduction of the salivary flow, up to 8 weeks following BoNT injections. This success rate gradually declined to 50% between the 8th and 16th week of assessment and approximately remained at that level for the rest of the official duration of the study (Fig 11.2).

Figure 11.2: Mean Submandibular Salivary Flow in Time



Clof =carrying the last observation forward, N = number of patients, Baseline: Measurement at baseline, Scopol: Measurement during scopolamine application, Washout: Measurement after Washout, BoNT_X: Measurements at subsequent moments (in weeks) following BoNT injections.

The data only allowed analysis up to 24-week after the BoNT injections, because an increasing number of parents lacked sufficient motivation to come for further assessment after that point. However, data were collected from 30 patients until 32 weeks, whereas 16 patients continued until 40 weeks after the BoNT injections. Eight patients came for follow-up visits until 48 weeks after the injections. A time curve of the SubFl was constructed starting at baseline with the mean value of the 30 patients that continued to BoNT-32 (Fig. 11.1). The resultant curve shows the same course, as was the case for the whole population (Fig. 7.2), which supports the consistency in our findings. In addition, the mean of the data of the remaining 16 patients at BoNT-40 and of the 8 patients at BoNT-48 were added (Fig. 11.1). The mean of the data of the thirty patients at BoNT-32 showed marginal significance compared to baseline. Although the number of patients, at BoNT-40 and 48, was too low to execute proper statistical analysis, the trend of the curve is promising. It indicates that the length of the effect of BoNT injections might be in the same range as is found for the treatment of hyperhidrosis. In theory this would mean that the majority of the patients could benefit from treatment more than a year. Further research is needed to confirm this and disclose the ultimate duration of the BoNT effect on the salivary glands.

11.2. The injection sites

We choose to inject the submandibular glands. These are the main paired glands producing about 70% of high viscosity, resting saliva[1]. In addition, resting saliva is composed of secretions from the parotid glands (~ 25%) and the sublingual glands (~ 5%). The large parotid glands are capable of producing great amounts of watery saliva that is secreted promptly as a reaction to tactile or gustatory stimulation of the oral mucosa for example during eating or drinking. In general, authors agree that the amount of saliva production is normal in CP. This study confirms the assumption that the submandibular glands contribute for a substantial amount to the total saliva production when a person neither eats nor drinks. Nearly half of the patients had a submandibular flow that was 60 to 75% of the total salivary production. It is estimated that only 25% of the resting saliva production would remain if the submandibular and sublingual glands would be inhibited bilaterally[2].

The treatment of drooling only by BoNT injections into the submandibular glands as a first step in treatment seems to be a reasonable approach, which was proven to induce substantial reduction of the salivary flow in resting conditions. However, others describe injection techniques for the submandibular glands as well as the parotids.

There is an increasing clinical acceptance to inject the parotid glands. This approach is frequently justified by the fact that the parotids are the largest salivary glands and easy to access. From an anatomical point of view this seems to be a valid argument. However, the size of the parotid gland is primary related to the specific capacity to produce large amounts of serous saliva at functional moments, e.g. during the processing of food or drinks. In principal, great precaution should be paid to the saliva production coming from the parotid glands. Reduction of it might have a negative influence on feeding and deglutition, which will be of disadvantage for some patients. Therefore, injections in the parotid glands should be avoided as a first choice of therapy in drooling children with CP. If, in the approach to treat drooling is chosen for BoNT injections, a two-step approach is justified. The submandibular glands are the first to be injected bilateral, followed by optional injections in the left or right parotid gland(s) if the clinical effect appears to be insufficient. The development of clinical guidelines on this issue is subject for further research.

11.3. Compensatory reactions from other glands

Surgical procedures are widely used in the treatment of drooling, which was summarized in chapter 1. The 'rerouting of Wharton's duct' or 'excision of the submandibular glands' are examples. In principle, these interventions are aimed to establish a definite reduction of the salivary flow. However, earlier investigations (unpublished) have settled the clinical idea that the parotid glands compensate for the diminished salivary flow. It is believed that this process starts after several months.

In this study, only the submandibular glands were injected with Botulinum toxin. Because of knowledge of the above-mentioned phenomenon, salivary flow rates from all major salivary glands, including the parotid glands, were obtained to be able to determine any compensatory reaction.

The curves of the submandibular flow (SubFl) as well as the total salivary flow (TSFl) were constructed (Fig. 7.2). The curves show the same pattern from washout up to 24 weeks after BoNT injections. A compensatory reaction from the parotids would be clear from an increasing slope in the TSFl-curve at some moment after BoNT injections. Nevertheless, great resemblance in pattern exists in the curves of SubFl and TSFl. An increase in the parotid flow because of a compensatory reaction following BoNT injections was not demonstrated during the entire duration of the study. Extended observations are needed to be conclusive on this point, which will also be subject for further research.

11.4. Response or non-response to therapy

Success to therapy was defined in three different ways, each closely related to the outcome of separate parts of the study.

The first research question was:
Does BoNT influence the function of the salivary glands?
Beyond any doubt, salivary flow is one of the main factors contributing to the amount of drooling. A reduction in the salivary flow, a physiological parameter, would be indicative of the anticholinergic action of the tested intervention within the glandular parenchyma. Compared to baseline the SubFl showed a mean reduction of 24.7 % during scopolamine application and a mean reduction of 42.4 % 2 weeks after BoNT injections. This reflects the explicit anticholinergic effect of BoNT. The SubFl remained significantly different from baseline throughout the study
In first instance, the definition of 'success to therapy' was limited to the question whether or not saliva secretion by the salivary glands changed after the interventions.

*First definition of response: a subject is assigned as a responder if minimally a 30% reduction is achieved in salivary flow compared to baseline. This reduction has to be present in at least 1 out of 3 of the BoNT measurements at 2, 4 or 8 weeks after BoNT injections**.

Frequency analyses were executed. Success to scopolamine was achieved in 94.9 % of the children. Success rates for BoNT were 69.2% two weeks after BoNT injections and 48.7% after twenty-four weeks. If the number of responders to scopolamine is compared to the BoNT-2 result, the outcome is in favor of scopolamine. However, we looked at the data in further detail. From this, it became clear that the majority of non-responders at BoNT-2 were very close to our demand of a '30% reduction of baseline salivary flow'. Nevertheless, from a pure methodological point of view these results can be attributed to measurement error (chapter 4).
In theory the difference in response rate can be explained in several ways: 1) the reaction to BoNT may be dose related. We did not investigate this because dose finding was not an aim of this study, 2) BoNT (or part of it) was not injected in the gland. However, ultrasound guidance assured adequate delivery and 3) immunity existed for BoNT. We did not rule out this possibility, although, the risk of neutralizing anti-BoNT type-A antibodies was low because none of these patients had previously been treated by Botulinum toxin.

**The 30% demand is explained by the estimated measurement error in the repeated baseline series of salivary flow rate measurements (chapter 4).*

The second research question was:
Does drooling diminish substantially when the salivary flow rate changes?
The cause of drooling is determined multifactor. Aspects like tongue trusting, the anatomy of the oral region, lip closure, reflexes, and muscular tone play a role in the severity of drooling. In addition, factors like age, general health, and mental abilities play an important role.
The clinical outcome in this study was evaluated by the drooling quotient, an observational method investigating drooling during a limited period of time (chapter 8: assessment). Based on the Drooling Quotient 'success to therapy' was defined.

Second definition of response: a subject is assigned as a responder if minimally a 50% reduction in Drooling Quotient is achieved, compared to baseline. This reduction has to be present in at least 1 out of 3 of the BoNT measurements 2, 4, or 8 weeks after BoNT injections.

It was decided that a 50% reduction in the DQ reflected a clinical relevant change. The submandibular glands produce about 60 to 70% of baseline salivary flow. In the event the DQ is reduced by 50% after BoNT injections, the change of flow from the submandibular glands, being the only gland exposed to this intervention, must have added substantially to this reduction. It must be noticed that scopolamine was applied transdermally by the patches. This means that scopolamine was available via the vascular system and reached the parotid glands also. During scopolamine 53% of the patients were recognized as responders. Response rates to BoNT were 64.1% two weeks after BoNT injections and 48.7% after twenty-four weeks.

To investigate the coherence between the two definitions of success to therapy a third definition was used.

Third definition of response: a subject is assigned as a responder if minimally a 30% reduction in salivary flow in combination with a 50% reduction in DQ is achieved, compared to baseline. This reduction had to be present in at least 1 out of 3 of the BoNT measurements 2, 4, or 8 weeks after BoNT injections.

The overall percentage of responders was 74.4% (29 out of 39 patients). The response rates are summarized in Table 11.1. The conclusion is that the majority of the patients reacted well according to the third definition.

Table 11.1: The response rates according to three definitions for response

	BoNT-2		BoNT-4		BoNT-8		Overall	
Definition	Resp %(N)	Non-resp %(N)	Resp %(N)	Non-resp %(N)	Resp %(N)	Non-Resp %(N)	Resp %(N)	Non-resp %(N)
Def. 1	69.2 (27)	30.8 (12)	64.1 (25)	35.9 (14)	61.5 (24)	38.5 (15)	94.9 (37)	5.1 (2)
Def. 2	64.1 (25)	35.9 (14)	43.6 (17)	56.4 (22)	53.8 (21)	46.2 (18)	79.5 (31)	20.5 (8)
Def. 3	48.7 (19)	51.3 (20)	38.5 (15)	61.5 (24)	43.6 (17)	56.4 (22)	74.4 (29)	25.6 (10)

As stated above, several factors might influence the frequency and severity of drooling. A non-response to therapy could be the result of insufficient reduction of salivary flow but could also be caused by other (confounding) factors that deteriorate drooling. On the other hand the situation can arise that patients with only a slight change in their salivary flow, demonstrate an unexpected improvement in drooling, which can be caused by modifying factors. These factors might be recognizable characteristics of the patient such as age, gender, developmental age, the anatomy of the oral region, movement disorder (reflexes and grimaces), epilepsy, or the combination of epilepsy and medication, and other factors like thumb-sucking. Another group of contributing factors could be more detailed symptoms for which a careful examination was made of anatomy (malocclusion), oral motor performance (insufficient lip closure, tongue trusting, uncoordinated tongue movements, tongue fasciculation), oral muscular tension (hypertonia/hypotonia), oral reflexes (hyper-reflexes/persisting pathological reflexes), oral sensitivity (hypersensitivity/hyposensitivity), speech (dysartria), and swallowing (dysphagia).

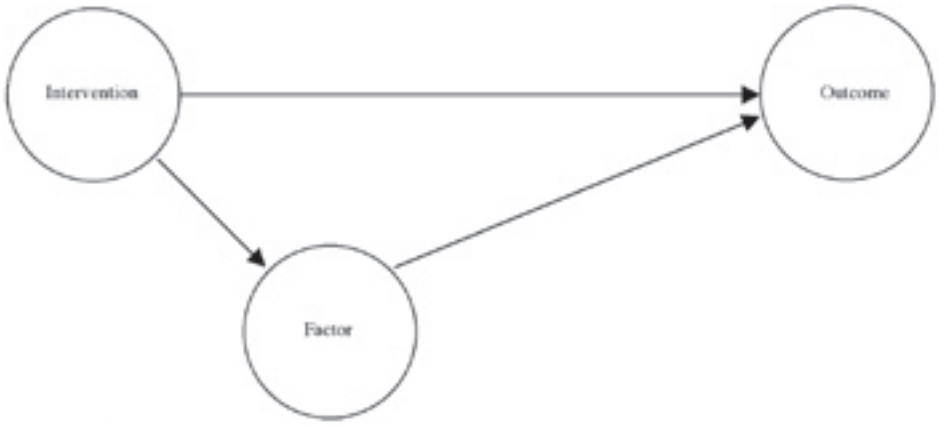
Prior to analysis the factors were graded according to their expected influence on the outcome of the interventions (Table 11.2). For example the item 'movement disorder' (sub-divided into pyramidal/spastic CP, extra pyramidal/athetoid CP, or a mixed CP) was expected to have explicit influence on the outcome. Repeated clinical examination by the speech therapist indicated that subjects with athetoid movement disorders and their facial grimaces had more stimulation of the parotids (not treated in this study) and consequently more severe drooling even after BoNT injections in the submandibular glands. Another example would be 'malocclusion'. It was expected that treatment for drooling would be less effective in the presence of malocclusion.

Table 11.2: Theoretical influence of patients' characteristics on drooling

	Grading of expected level of influence on response to therapy		
Factor	**Low**	**Mediate**	**High**
Age		X	
Gender	X		
Dev. Age			X
Mov. Disorder		X	
Epilepsy	X		
Epilepsy + Medication		X	
Lip closure			X
Tongue trusting			X
Tongue fasciculation	X		
Malocclusion			X
Oral hypertonia		X	
Oral Hypotonia			X
Oral Hyper-reflexes			X
Pers. Pathol. Reflexes			X
Disturbed oral sensibility			X
Dysartria		X	
Dysphagia			X

In the 2nd and 3rd definition of 'response' these factors are incorporated. The central question was whether or not these biological and physiological factors influenced the relation between intervention and outcome in terms of response or non-response of which the theoretical concept is depicted in Figure 11.3.

Figure 11.3: Conceptual interactions of intervention and confounders with outcome



From a methodological point of view it could be stated that factors influencing the outcome of responders versus non-responders could either act as a 'modifier' or as a 'confounder'. Modifiers enhance the result while confounders inhibit it. In this sense the outcome of the interventions is a function of the intervention itself as well as the influencing factors. The challenge was to split the joint variance of the intervention and the individual factors.

In first instance, it was calculated what sample sizes would have been actually needed, demanding an Alpha 0.05 and a Power 0.8, to be able to make statements about this issue. To execute an uncorrected chi-square test, 47 case and 47 controls would have been needed. To do a corrected chi-square test or a Fisher's exact test, 56 cases and 56 controls were needed.

The population of this study did not meet these requirements. For this reason, a result of analysis of modifying or confounding factors would provide a 'low grade evidence'. All variables listed in table 11.2 were analyzed in relation to the outcome: response versus non-response. None of the factors demonstrated significant influence on the outcome. In this study 39 patients received BoNT injections, of whom 29 were responders and 10 non-responders, according to the 3rd definition.

Given the sample size of 39 case and 39 controls, it could not be concluded whether or not any of the identified factors was of influence on the outcome of response to therapy.

11.5. Changes of the parenchyma

Chemo-denervation, as introduced by BoNT injections, theoretically leads to degeneration of the glandular parenchyma. Based on this, it is expected that repeated BoNT injections might give increasingly hypotrophy resulting in a longer effect of the injections. In the course of the present study all patients underwent BoNT treatment under ultra-sound guidance. According to standardized methods cross-sectional digital pictures of the submandibular glands were made in different directions. The majority of the patients were seen for evaluation at the department of radiology, however at variable time intervals. Thus, no definite conclusions could be drawn from these data. Nevertheless, the impression exists that the volume of the injected glands had decreased and the ultra-sound density was changed several months after BoNT injections. This is subject for further research.

11.6. Side effects

Side effects due to scopolamine became apparent within the first three days of administration and were reported in 82.2% of cases. Several patients complained of more than one symptom. Most often reported adverse effects were xerostomia (66.7%), restlessness (35.6%), somnolence (35.6%), blurred vision because of pupillary dilatation, and confusion (20%). Four out of the six dropouts from the study had to end their participation because of adverse effects to scopolamine. In all four cases, restlessness, apparent in their movement performance, and confusion were the main reasons to terminate scopolamine use.

Following BoNT injections, incidental side effects were reported. Two patients (5.1%) had a transient flu-like syndrome. Another 3 patients complained of mild difficulty with swallowing.

Many side effects are seen during the use of anticholinergic drugs, which makes this group of drugs unsuitable for long-term use in the treatment of drooling.

With respect to the magnitude and the duration of effect, Botulinum toxin has a favorable outcome.

11.7. Treatment strategy

The goals of any treatment of drooling will always be the reduction of visible anterior drooling or a decrease of posterior drooling. The first step in investigation should include a thorough evaluation and instruction by the speech therapist focused on oral stimulation, and eating and drinking programs. Prior to intervention, repeated

evaluation of the cause of drooling should be undertaken with special attention to the pharyngeal and esophageal phase of swallowing. In cases of impaired swallowing the danger of posterior drooling and aspiration should be considered.

The literature is not unequivocal with respect to the outcome of the different therapeutic approaches. Neither conservative treatments nor surgical procedures seem to be universally successful. In general, surgery is recommended only if conservative measures fail to reduce drooling.

The application of anticholinergic drugs to treat drooling should only be advised incidentally. It is defensible to prescribe scopolamine or another anticholinergic drug with less central side effects (e.g. glycopyrrolate), for moments that an individual wishes to be without drooling. This should not last longer than one or two days.

In the dispute Botulinum toxin injections are new. No guidelines exist to position BoNT injections among conservative measure or surgical interventions. There is no medical restriction to use BoNT in very young children. However, up to the age of four years conservative measures (excluding medication) could be the first choice to treat drooling in complex handicapped children. Drooling beyond the age of 4 is regarded as definitely pathologic. If conservative treatments fail and drooling does not subside after the first dentition has been completed, invasive therapy can be considerate. Between the age of 4 and 7 years BoNT might be in favor of surgical procedures. BoNT injections into the major salivary glands can be safely executed provided that ultrasound guidance is used during the procedure. The effect is temporary, although it might be more than a year. This offers a good opportunity to observe the clinical relevance or adverse effects of a reduction in salivary flow in any particular child. Besides, the possibility exists that drooling will diminish substantially after dental aging. It is imaginable that a drooling child is repeatedly treated with Botulinum toxin during several years. After this period, dentition is completed which possibly diminishes drooling.

Surgery to the salivary glands should at least be preserved for the age of 7 and older. By that time the anatomical relations in the oral region are evident and the problem of the drooling is clear. Rerouting of Wharton's duct should always be avoided in the presence of posterior drooling.

A challenge is to find out what child characteristics are decisive for the extent of drooling and the response to specific interventions (speech therapy, BoNT injections, rerouting of a duct) in a larger population.

11.8. Methodology and Statistics

11.8.1 The design

Regarding the population, it was expected to meet inter-individual and intra-individual variability on relevant parameters (salivary flow rate and Drooling Quotient) during the study. To control variability among and within subjects in a randomized clinical trial a large number of patients had to be included, which would not be available within the time limit of this study.

In a crossover design the demanded number of patients would be considerably lower, although the risk of a "carry-over" effect would exist. Regarding the known pharmacological properties of scopolamine we could exclude a carry-over effect from scopolamine to BoNT with certainty, provided an adequate washout period of 72 hours was taken into account. In the event, BoNT treatment would come prior to scopolamine a carry-over effect could not be excluded because the duration of the BoNT effect was unknown at start of the study and subject of investigation. This demanded a strict sequence of treatment: scopolamine before BoNT.

We performed a controlled, open-label, clinical trial with an intention to treat (ITT).

11.8.2 Patient selection, Control of bias and blinding (masking)

All patients were included as consecutive subjects recruited mainly by (in)direct advertisement. There has been no specific selection before the first outpatient visit.

A good level of control of bias was achieved by using the same group of patients (within subject design) for the experimental treatment (BoNT) and the control treatment (scopoderm). This reduced the problem of between-subjects variation between the experimental and control group. The within-subject variation was counted with by estimating (computer program) the number of patients large enough to reach and adequate power.

Two independent employees, handling essential data (the results of salivary flow, drooling quotient, and questionnaires) were both blinded to the status and timetable of the participating patients. This essential condition was supported by the introduction of a scheduled variation in the number of baseline measurements that had to be obtained from each child. Besides, the data were related to a registration number and not to a specific name.

11.8.3. Dropouts

Because this study was executed with an "intention-to-treat" a thorough description of dropouts was demanded.

A patient that did not meet the inclusion criteria or demands of the qualification period was not regarded as a dropout. Failure of a patient to continue the study, for whatever reasons, after start of scopolamine treatment was considerate a 'dropout'. However, the protocol anticipated for the possibility that some of the subjects might not fulfill the scopolamine period, because of side effects. The occurrence of side effects was regarded as an outcome of the study because this could be decisive whether one treatment would more beneficial above the other. If, the application of scopolamine was discontinued within 48 hours from start the patient was regarded as a dropout. If, however, the use of scopolamine lasted more than 48 hours the subject could remain in the study provided a control measurement of salivary flow and the drooling quotient was obtained within 24 hours (the washout of scopolamine takes 72 hours). Patients with scopolamine application longer than 48 hours but a delayed control

Visit, of over 24 hours, were excluded from the study.

After BoNT injections, patients had to fulfill control measurements at 2, 4, 8, 16, and 24. In case a subject could not attend any of the control visits at 2, 4, or 8 weeks exclusion followed. Furthermore, it was the demanded that at least 3 out of the 5 control-visits were attended. Other reasons for exclusion were: 1) introduction or change of medication that could possibly influence salivary secretion, and 2) complicating disease. If, at any time of the course, parents refused further cooperation the child was considered to be a dropout and the data were handled accordingly. In these situations, specific efforts were made to approach the patient and the parents according to 'good clinical practice'.

11.8.4. Handling of data

The database comprised repeated scores of salivary flow rate, the drooling quotient, the teacher drooling scale, visual analog scales, and the results of Quality of life questionnaires. Additional data were collected only at the first history taking and examination, like: anatomy of the oral and nasal region, motor activities of tongue and oral cavity, tactile sensitivity, muscular tone, and reflexes.

For some analyses, missing data of submandibular salivary flow, right or left parotid flow rate, and drooling quotient were interpolated according to a 'carrying the last observation forward'-system (CLOF) or a 'worst case scenario' (WCS).

For the 'carrying the last observation forward'-data the following rules were applied for each individual patient:

- If a score in the Scopo-derm" period was missing the data was completed with the mean of the BoNT scores at 2, 4, and 8 weeks.
- If washout scores were missing it was completed with the baseline value.
- If a BoNT-2 score was lacking the Scopo-derm" value was filled in.
- In case any of the BONT 4, 8, 16, and 24 scores were missing this was completed with the former score.
- In case, particular scores were missing of more than 10 subjects the data were removed from the statistical analysis.

For the 'worst case scenario'-data the following rules were applied:

- In case a score was missing for Scopo-derm" this was completed with the lowest score at 2, 4, and 8 weeks of the BONT-series of the same patient.
- Washout missing data were completed with the baseline score.
- If any of the BoNT scores were missing the baseline value was applied in the analysis.

11.8.5. Analysis of the data

The inclusion criteria and exclusion criteria for this study were clearly defined (Table 1.3). Dropouts and those lost to follow-up were extensively described. Thus, all patients that were excluded from the study were explained dropouts. Four could not fulfill the scopolamine period, 1 patient received additional medication, and one patient became sick, which was not related to the interventions of the study. These six patients had in common that they dropped out of the study before the BoNT injections were given. Therefore, these patients only ended the control treatment and did not participate in the experimental treatment of which, consequently, no data were available. Given the fact that there was an intention to treat, the data of the dropout patients were eliminated from the database.

Several ways of analysis could have been executed in the database. A per protocol analysis should have been executed in the original data. In a first overview of the database (frequency analysis and scatter diagrams) it was found that list-wise missing data were randomly distributed over the measurement moments and patients. In the event of random missing data this could mean loss of power because subjects with many missing data are excluded from distinguished parts of the analysis. Based on this, it was decided not to perform a per protocol analysis but to replace missing data

by adjusted data and to perform a "best-case" (clof) and "worst-case" (wcs) scenario analysis.
The wcs analysis, in fact, equals an "intention to treat" analysis (ITT).
The "in treatment" analysis was done with data that were adjusted according to the system of "carrying the last observation forward" in which basically each missing data point is replaced by the score prior to it.
After all, there remains a risk that the treatment effect is overestimated. Therefore any calculated result in the clof analysis was compared to the outcome of the wcs analysis. Resemblance in both outcomes was interpreted as strongly supportive for the treatment effect.
It seems reasonable to argue that the true effect in this population is somewhere between the outcomes of these approaches.

11.9. Future research

Although, this study has provided evidence for the positive effect of BoNT injections on severe drooling in patients with cerebral palsy, many questions remain unanswered.
Does hypo-trophy of the salivary glands occur after repeated BoNT injections?
What child characteristics are decisive for the severity of drooling and how is their mutual relation?
What child characteristics are decisive for a good response to the different treatment modalities?
How to decide for either BoNT injections in the submandibular glands, or in both the submandibular and parotid glands?
Investigations should be made on the incidence and the magnitude of the problem of posterior drooling.
The development of clinical guidelines to position intra-glandular BoNT injections among conservative measures and surgical interventions is most essential.

Drooling has to be considerate as one of the essential problems in the care for children with cerebral palsy. Their treatment is of major importance for the psychosocial well being of the involved child and his or her parents or caretakers. Expert teams that evaluate and treat this problem should consist of a speech therapist, physiatrist, child neurologist, and ENT surgeon. In addition, the possibility to consult a cranio-maxillo-facial surgeon, an orthodontologist, and a dentrist with experience in the care for handicapped patients is needed.

References

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Summary

Samenvatting

Summary

Chapter 1

Severe drooling in children with cerebral palsy forms the central theme of this thesis. This condition occurs approximately in one of three children with CP. Persisting drooling, being pathologic after the age of four, is difficult to treat and it results in a socially disabling condition for the child and its primary caretakers. It is generally caused by a poorly developed mechanism of coordination of oro-facial, palato-lingual and head and neck musculature.

Therapy comprises behavioral techniques, speech therapy, training of oral motor skills, anticholinergic drugs, and surgical procedures of which none is universally successful. Botulinum neuro-toxin type-A (BoNT) is a new option in the treatment of drooling. In the present study, a controlled clinical trial has been conducted that evaluates the treatment of drooling by comparing the efficacy of BoNT (experimental treatment) to an anticholinergic agent (control treatment with scopolamine). This study is based on the fact that Botulinum Toxin causes pre-synaptic inhibition of cholinergic nerves endings. The difference in effect on drooling between scopolamine and BoNT® is tested.

Chapter 2

Anticholinergic drug treatment for drooling is widely described in the literature. This chapter describes the results of a systematic literature review searching for evidence of efficacy of anticholinergic drugs in the treatment of drooling. Only few studies of the identified studies were designed good enough to allow conclusions. Given the number of studies that could be selected and their design, the evidence of efficacy of anticholinergic drugs in the treatment of drooling is low. A meta-analysis could not be performed from the selected reports and no individual anticholinergic drug could be assigned as 'the' standard therapy.

Reviewing the literature, it is concluded that all drug treatment options have their limitations. In general, side effects during long-term use constitute a serious problem in the treatment with anticholinergics, often necessitating to stop therapy.

Chapter 3

A study among 62 healthy non-drooling school children (age 6 - 11 yr) was conducted in order to obtain reference data of salivary flow. Sialometry was done by using the swab method of which the reproducibility appeared to be good. The test-retest reliability was significant. As one of the results of this study it was concluded that the magnitude of salivary flow rates was not influenced by age or gender. The outcome was in accordance with earlier reports. Lead by the experiences of this study it was decided to use "the swab method" in subsequent investigations.

Chapter 4

This chapter describes the outcome of repeated baseline measurements of salivary flow rates in multiple handicapped children. The objective was to test the potential clinical applicability of the swab method in handicapped children. Two speech therapists were trained to use the swab method. They performed a series of baseline measurements of salivary flow. The 'Bland and Altman' method, especially designed for analysis of repeated measurements, was applied. The within-subjects standard deviation (SW) was calculated because it would express the magnitude of measurement error and biologiacal variation. The estimated SW (0.11 ml/min) appeared to be about 25% of the mean salivary flow rate. Consequently, the change in the salivary flow after an intervention to treat drooling should exceed this 25% before the effect can be attributed to the treatment.

Chapter 5

An 'in-vitro' as well as an 'in-vivo' pilot study was executed to evaluate the technique of the BoNT injections in the salivary glands.

The in-vitro study revealed that the lobular subdivision of the glands is essential. To gain adequate spread of BoNT through the glandular parenchyma a total volume of at least 1.0 ml should be fractionated over two or three injection sites.

Ultrasound visualization, used during the injections in the in-vivo study, is thought to be essential because it guides the injection needle, making it possible to inject BoNT at the proper place. It is the only possibility for real-time control to assure an optimal clinical result. Adequate ultrasound guidance prevents BoNT from being injected into structures that surround the glands, e.g. the musculature. The possible consequences of a false route are discussed in the chapter.

Additionally, the use of general anesthesia in youngsters, aging 4 to 16 years, is

recommended to avoid improper injections because of restlessness and movements, due to fear or the primary movement disorder of the patient.

Chapter 6

A pilot study (N = 3) was undertaken to explore the feasibility of the proposed protocol of the salivary flow measurements and the BoNT injections, which were described in chapter 5. The measurement procedures and the injection technique were well tolerated by all three participating children. Compared to baseline, salivary flow was maximally reduced by 51 to 63%. The clinical outcome and the parents' comments encouraged continuing with a larger study.

Chapters 7 en 8

The core of the study is dicussed in these chapters.

In 2000 and 2001, 53 severely drooling children with a CP were seen in the outpatient clinic. The inclusion criteria are presented in Table 1.3. Forty-five children were included in the trial, during which the effect of BoNT (the experimental intervention) on salivary flow and drooling was compared to scopolamine (the control intervention). Figure 1.8 (also Figure 7.1) clarifies the dropouts and the number of patients in each phase of the study. The results of 39 children could be analyzed.

The salivary flow rate and severity as well as frequency of drooling were measured. After inclusion, children were measured subsequently during baseline, a 10-days period of Scopoderm-TTS® treatment, a washout period, and after BoNT injections.

The central question was whether scopolamine and BoNT had distinguishable effects on the salivary flow rate from the injected glands. To evaluate this the saliva production was measured at baseline and after interventions.

Analyses of variance were used to evaluate the differences between the subsequent measurements. For all results an adequate level of significance was demanded ($p \leq 0.05$).

In chapter 7 it is concluded that both, scopolamine and Botulinum toxin, had a good anticholinergic effect within the parenchyma of the submandibular gland. Among the participating children, both treatments resulted is a significant reduction of the salivary flow rates when compared to baseline. Responders to BoNT achieved a reduction in submandibular salivary flow by far exceeding that of scopolamine. This reflected the explicitly strong anticholinergic effect of BoNT. Compared to baseline, the submandibular salivary flow showed a mean reduction of 24.7% during scopolamine application

and a mean reduction of 42.4% two weeks after BoNT administration. The greatest reductions in salivary flow were achieved 2, 4, and 8 weeks following BoNT. Throughout the study, the salivary flow remained significantly lower compared to baseline. Flow measurements 2, 4 and 8 weeks after injections, demonstrated significantly greater reductions in the mean salivary flow rate compared to scopolamine.
A 30% reduction of baseline salivary flow rate was demanded for a child to be assigned as a responder*. According to this definition, the success rate to scopolamine was ~95% of the population and ~70% to BoNT. Explanations for this differences are dicussed in the chapter.
Because of the prerequisites that are formulated in the inclusion criteria (diagnosis and the degree of drooling) the results of this study cannot be straightforwardly generalized to any other population. In theory, however, it is expected that the physiological effect of intra-glandular BoNT injections will be present in any population, provided no glandular diseases or abnormalities are present.

Chapter 8 presents the second part of the clinical trial . The objective was to evaluate the effect on clinical apparent drooling of the application of scopolamine compared to BoNT injections. Drooling was measured by means of the 'Drooling Quotient", an observational semi-quantitative method. In addition, the parental opinion was evaluated by means of the Teacher Drooling Scale and by the use of Visual Analog Scales. Analysis of the data prior to and after intervention demonstrated significant differences in drooling. BoNT injections reduced drooling for at least 6 months for a large part of the population.
The response rate to therapy was estimated according to our definition of success. A reduction of 50% of baseline drooling was demanded to assign a patient as a responder to therapy. The outcome demonstrated good results for BoNT (~64%) and scopolamine (53%).
In the discussion of the chapters 7 and 8 the advantages and disadvantages of the two drooling treatment modalities (scopolamine and BoNT) are discussed. Many side effects are seen during the use of anticholinergic drugs, making this group of drugs unsuitable for long-term use in the treatment of drooling. With respect to the magnitude and the duration of effect as well as the few side effects, Botulinum toxin has a favorable outcome.

**The 30% demand is explained by the estimated measurement error in the repeated baseline series of salivary flow rate measurements (chapter 4).*

Chapter 9

This chapter presents a case study in which the problem of posterior drooling is described. Posterior drooling in the presence of impaired swallowing bears the risk of saliva aspiration. BoNT injections injected in the salivary glands were effective to decrease the amount of swallowed saliva resulting in a remarkable improvement of the clinical condition. After repeated treatments, the patient experienced no aspiration pneumonia anymore.

Chapter 10

A questionnaire was developed, containing items of quality of life. The selected items, concerning daily situations and daily care, were regarded a representative aspects of quality of life in relation to the clinical problem of drooling. Parents were asked to fill in lists at pre-scheduled time-intervals throughout the study. The outcome of this study demonstrates significant improvement on the majority of the items as a result to therapy. Daily care becanme less demanding and a lower rate of damages to computers and communication devices was recorded.

This study proved that reduction in salivary flow and a diminished drooling has significant and relevant effects on aspects of QoL of both the participating children with CP and their parents. It is recommended that all interventions to treat drooling (surgery, medication, behavior therapy, etc.) be evaluated not only on primary variables such as the salivary flow, but also on consequences for QoL.

Samenvatting

Hoofdstuk 1: algemene inleiding

Het centrale thema van dit proefschrift is het kwijlen bij kinderen met een cerebrale parese (CP). Kwijlen wordt in de literatuur ook wel omschreven als 'onwillekeurig speekselverlies uit de mond', hetgeen normaal is bij opgroeiende kinderen tot de leeftijd van ongeveer 18 maanden. Aanhoudend kwijlen na de het vierde jaar wordt als pathologisch beschouwd.

De incidentie van kwijlen bij kinderen met een CP wordt in de literatuur verschillend opgegeven. Ook de wijze waarop de speekselproductie en het kwijlen worden beoordeeld loopt sterk uiteen. De speekselvloed uit de verschillende speekselklieren en de ernst van het kwijlen zijn moeilijk in maat en getal uit te drukken. De speekselproductie kan van minuut tot minuut variëren en wordt beïnvloed door factoren zoals honger, dorst, vermoeidheid, angst en opwinding. Samengevat kan gesteld worden dat circa 30 % van de kinderen met een CP in lichte tot ernstige mate kwijlt. Het kwijlen vormt een sociaal probleem voor kind en gezin veroorzaakt door de onesthetisch aanblik en onaangename geur. De verstaanbaarheid van de spraak wordt negatief beïnvloed. Kwijlen werkt stigmatiserend. Kwijlende kinderen met een normaal mentaal vermogen worden vaak op een lager niveau aangesproken. Zestien procent van de ouders van kinderen met een CP geeft aan dat het kwijlen, afgezien van de emotionele en sociale belasting, een dagelijks terugkerend probleem is met intensieve verzorging, zoals het bij voortduring afvegen van het mondgebied, aansporen tot slikken en verschonen van slabben en kleding.

Naar schatting heeft eveneens 1/3 van de kinderen met een CP een gestoorde mondmotoriek met onvoldoende of inefficiënte tongbeweging, onvolledige lipsluiting, een lage slikfrequentie, een verlaagde gevoeligheid in het mondgebied en verlaagde of pathologische reflexen. Kwijlen bij kinderen met een CP ontstaat in principe door een slechte verwerking van het speekselaanbod in de mond en is over het algemeen niet het gevolg van een verhoogde speekselproductie. Door een slechte coördinatie van de spieren die betrokken zijn bij het slikken verzamelt zich speeksel in de wangzakken, onder de tong of in de hypopharynx met als gevolg speekselvloed aan de lippen (anterior drooling) of ongecontroleerde overloop in de achterste keelholte (posterior drooling).

De behandeling van kwijlen heeft altijd als doel het zichtbare speekselverlies of de mate van posterior drooling te verminderen. De interventies kunnen feitelijk in drie categorieën worden onderverdeeld (zie ook: tabel 1.1):

- Conservatieve behandeling
- Invasieve/niet-chirurgische behandeling
- Chirurgische behandeling

De conservatieve benadering is er op gericht om het speeksel in de mondholte beter te verwerken. Dit verschilt van de chirurgische benadering waarbij het doel is de speekselvloed te verminderen door verwijdering van een van de klieren, of het speeksel op een andere plaats in de mond aan te bieden zodat het beter weggeslikt kan worden. De invasieve/niet-chirurgische behandeling is er op gericht de speekselproductie te verminderen. Bij deze benadering wordt de innervatie van de speekselklieren beïnvloed. De behandeling van kwijlen middels injecties met Botuline Toxine in de speekselklieren is hier een voorbeeld van en vormt de experimentele behandelmethode die is onderzocht in dit promotieonderzoek.

De hypothese van dit onderzoek is gebaseerd op het gegeven dat Botuline Toxine (BoNT) de prikkeloverdracht van cholinerge zenuwuiteinden naar het doelorgaan remt. De postganglionaire parasympathische zenuwen, die de speekselklieren innerveren, zijn voorbeelden van dergelijke zenuwen. Van BoNT zijn meerdere subtypen bekend, waarvan het Botuline toxine type-A het meest wordt toegepast. De werking van BoNT berust op het feit dat het molecule, bestaande uit 2 ketens van eiwitten, in staat is om aan het pre-synaptische uiteinde van de postganglionaire parasympathische zenuw te binden en via een proces van endocytose in het cytoplasma binnen te dringen (figuur 1.6a t/m e). Daarna wordt het BoNT gesplitst in een lange en een korte keten. De korte keten is het actieve deel dat zich kan binden aan SNAP-25 (synaptosomal associated protein), een enzym dat in het celmembraan nodig is voor het vrijmaken van de neurotransmitter 'acethylcholine'. Na binding van de korte BoNT-keten aan het SNAP-25 wordt de fysiologische reactie geblokkeerd en zijn de speekselklieren gedenerveerd. Theoretisch zou hierdoor de speekselproductie verlaagd kunnen worden. In dit promotieonderzoek is onderzocht of BoNT (experimentele behandeling), geïnjecteerd in de speekselklier, voldoende remmende werking op het speekselklierparenchym vertoont om een tot een klinisch merkbare afname van de speekselvloed te komen. Het effect van BoNT wordt vergleken met dat van het anticholinergicum 'scopolamine' (controlebehandeling).

Onderzoeksvragen:

1. Heeft BoNT invloed op de speekselproductie van de glandulae submandibularis?
2. Vermindert het kwijlen indien de speekselproductie afneemt?
3. Verbetert de kwaliteit van leven door de interventies?

Vanaf Januari 2000 werden 53 patiënten poliklinisch beoordeeld om de inclusiecriteria te toetsen (tabel 1.3). Uiteindelijk werden 45 patiënten, met een gemiddelde leeftijd van 9,5 jaar geïncludeerd.
Het onderzoek is goedgekeurd door de medisch ethische beoordelingscommissie van de regio Arnhem/Nijmegen (CWOM: Commissie Wetenschappelijk Onderzoek met Mensen).

Hoofdstuk 2: een literatuuranalyse: het effect van anticholinergica bij de behandeling van kwijlen

Dit hoofdstuk omvat een systematisch overzicht van de wereldliteratuur ('systematic review') waarin gezocht wordt naar bewijs voor de effectiviteit van anticholinergische medicatie bij de behandeling van kwijlen bij kinderen met CP. Een dergelijke 'review' is bedoeld om de uitkomsten van onderzoek dat reeds is verricht en gepubliceerd kritisch te analyseren en de resultaten te vergelijken.
Relevante publicaties werden met een computermatige zoekactie geïdentificeerd voor de periode van vóór juni 2002. Gebruik werd gemaakt van de zoekmachines in de Medline database (vanaf 1966), Pubmed (vanaf 1966), de Cochrane database en Current Contents (vanaf 1996). De gebruikte sleutelwoorden staan weer gegeven in tabel 2.1.
Er werden uitsluitend klinische studies geselecteerd die als doel hadden om bij patiënten het kwijlen te behandelen. De publicaties dienden in het Engels, Duits, Frans of Nederlands te zijn verschenen. Brieven, samenvattingen en verslagen van presentaties werden niet in de analyse opgenomen. Tabel 2.2. geeft de selectiecriteria voor de aangetroffen publicaties weer. De publicaties werden geblindeerd en door drie reviewers onafhankelijk beoordeeld en in een consensusbijeenkomst besproken aan de hand van een gestructureerde controlelijst (tabel 2.3). De eerste computerzoekactie leverde 64 publicaties op waarvan 36 werden afgewezen op basis van de samenvatting. Van 28 geanalyseerde publicaties werden 7 artikelen geselecteerd voor verdere analyse. Het betrof 3 'randomized clinical trials' (RCT), 3 cohort studies en 1 studie met een experimenteel design.

RCT's leveren vanwege het onderzoeksdesign de beste bewijskracht. Slechts 1 van de 3 RCT's kon de toets van de opgestelde criteria doorstaan. In de 'evidence synthesis' leverde deze studie, in relatie tot de onderzoeksvraag, 'hoge bewijskracht'. Een andere studie leverde 'middelmatig' bewijs en de laatste RCT 'laag' bewijs.
Cohort studies hebben minder bewijskracht maar kunnen secundair bewijs leveren indien een methodologisch goed verslag wordt gegeven. Eén van de gevonden cohortstudies was matig informatief over de effectiviteit van anticholinergica. De andere cohortstudies leverden onvoldoende of geen informatie op. De experimentele studie was goed opgezet en leverde expliciet ondersteunend bewijs.
Er bleken dus weinig publicaties te zijn die de effectiviteit van anticholinergica tegen kwijlen bewezen. Het uitvoeren van een evidence synthese was niet mogelijk omdat in de studies de bepaling van de speekselvloed en de ernst van het kwijlen te veel verschilden.
Geconcludeerd werd dat:

- een uitspraak over de bewezen effectiviteit van anticholinergica bij de behandeling van het kwijlen, bij kinderen met een CP, niet was te geven. In de klinische praktijk lijken anticholinergica het kwijlen bij kinderen met een CP wel te verminderen.
- voorts kon geen uitspraak worden gedaan over de langetermijneffecten van anticholinergica.
- tenslotte, anticholinergica geven altijd bijwerkingen zonder dat duidelijk werd in welk percentage van de gevallen bijwerkingen noodzaakten tot beëindiging van de therapie.

Hoofdstuk 3: speekselproductie bij gezonde kinderen
Bij 62 gezonde schoolgaande jongens en meisjes in de leeftijd van 6-11 jaar werd de ongestimuleerde speekselproductie gemeten teneinde een referentiegroep te creëren voor de kwijlende kinderen die behandeld zouden gaan worden.
Onderzocht werd of bij gezonde kinderen de leeftijd of het geslacht, invloed hadden op de speekselproductie. Er werd geen verschil gevonden in de productieniveaus van speeksel tussen jongens en meisjes. Ook bleek de speekselproductie niet beïnvloed te worden door de leeftijdsgrenzen waarbinnen gemeten is. Het niveau van de speekselproductie zoals gemeten aan de parotisklieren (0.15 ml/min) bleek groter dan wat in de literatuur wordt vermeld met andere meetmethoden. Het is mogelijk dat de wattenmethode enige tactiele stimulatie geeft op het moment dat de watten in aanraking komen met het wangslijmvlies. Het relatieve aandeel van de parotis

productie in de totale speekselproductie nam daardoor wat toe. De speekselvloed vanuit de glandulae submandibularis en sublingualis (0.32 ml/min) kwam overeen met de gegevens zoals die in de wereldliteratuur vermeld worden.
De reproduceerbaarheid van de metingen met de wattenmethode bleek goed te zijn ongeacht de speekselklier die werd onderzocht. Hoewel er per kind enige variatie bestond tussen het niveau van de 1ste en de 2de speekselmeting, werden geen significante verschillen gevonden voor de groep. Dit komt overeen met de resultaten van andere studies en ondersteunt het idee dat er voor gezonde kinderen geen sprake is van een leercurve in het accepteren van de watten in de mond.

Hoofdstuk 4: evaluatie van de meetmethode
In dit hoofdstuk is aandacht besteed aan een nadere analyse van de 'swab method' ofwel de wattenmethode. Met deze kwantitatieve meetmethode is tijdens dit onderzoek de speekselproductie onderzocht. De toepasbaarheid en de reproduceerbaarheid van de wattenmethode zijn getoetst omdat in de literatuur geen gegevens te vinden waren voor kinderen met een cerebrale parese of een vergelijkbare handicap. De statistische methode met de berekening van de 'within-subject standard deviation' (SW), zoals beschreven door Bland en Altman, werd toegepast om de meetfout (measurement error) en de biologische variatie van de speekselproductie (biological variation) te kunnen kwantificeren.
Voor analyse werden de gegevens gebruikt van 45 ernstig kwijlende kinderen. Er bleek een goede constantheid te bestaan tussen de waarden van speekselmetingen van opeenvolgende metingen. Bovendien waren duplo-metingen niet verschillend, hetgeen aangeeft dat de biologische variatie bij de gekozen opzet verwaarloosbaar was.
De SW werd berekend en bleek geschikt om de 'measurement error' en de 'biological variation' te kwantificeren. Op deze manier kon worden aangegeven in welke mate de speekselproductie moest veranderen om het effect van een uitgevoerde behandeling niet toe te schrijven aan meetfouten of de biologische variatie in de speekselproductie van de onderzochte personen.

Hoofdstuk 5: de techniek van het injecteren
Op basis van de farmacologische eigenschappen van BoNT wordt aangenomen dat het vrijkomen van acethylcholine kan worden geblokkeerd indien het toxine in het weefsel wordt geïnjecteerd en vervolgens de presynaptische uiteinden van de postganglionaire parasympathische zenuwen kan bereiken. Bij deze toepassing moet rekening worden

gehouden met ongewenste neveneffecten als het BoNT niet exact op de juiste plaats wordt gespoten en bijvoorbeeld in de omgevende structuren terechtkomt. Dit geldt met name voor de spieren die direct in de buurt van de speekselklieren liggen en betrokken zijn bij het slikken.

In dit hoofdstuk wordt verslag gedaan van een in-vivo studie en van een in-vitro studie.

Voor de in-vitro studie werd een speekselklier (glandula submandibularis) geïnjecteerd, die enkele minuten daarvoor bij een patiënt werd verwijderd tijdens een radicale nekdissectie. Het doel was om de verspreiding van BoNT in het parenchym te bepalen en vast te stellen hoeveel volume-eenheden van een Botox® (Allergan BV, Nieuwegein, Nederland) oplossing noodzakelijk waren voor

een adequate verdeling over de speekselklier. Tijdens de proef werd de klier gefractioneerd geïnjecteerd met Omnipaque. De samenstelling hiervan is vergelijkbaar met die van een BoNT oplossing. Er werd een serie röntgenopnamen gemaakt om de verspreiding te kunnen visualiseren (figuur 5.2.) Geconcludeerd werd dat de glandula submandibularis wordt onderverdeeld door septa hetgeen in relatie tot de therapie met BoNT relevant bleek te zijn. Om een goede verdeling in het klierweefsel te krijgen moeten tenminste 2 depots van de oplossing worden gespoten, waarbij een totaalvolume van 1 tot 1,5 ml wordt gebruikt om een adequate verspreiding in het weefselparenchym van de speekselklier te verkrijgen.

In de in-vivo studie wordt beschreven hoe de intra-glandulaire injecties met BoNT bij patiënten de patiënten werd uitgevoerd. Echografische controle van de injecties bleek nodig. De speekselkier kan hiermee goed in beeld worden gebracht. Een aantal primaire afwijkingen kan worden gediagnosticeerd. De injectienaald wordt gevisualiseerd tijdens het spuiten en foutieve deposities kunnen worden voorkomen.

Algehele narcose was nodig voor het adequaat uitvoeren van de procedure bij gehandicapte kinderen in de leeftijd van 3 tot 16 jaar. Onrust door angst of bewegingen door de primaire motorisch stoornis kan met algehele anesthesie worden voorkomen. Dit geeft de beste garantie dat Botox op de juiste plaats wordt geïnjecteerd.

De mogelijke bijwerkingen van foutieve injecties in het gebied naast de glandulae parotis en submandibularis zijn nader uitgewerkt.

Hoofdstuk 6: Botuline toxine injecties in de glandulae submandibularis: een pilotstudy
Het doel van dit studieonderdeel was het protocol van speekselmetingen en BoNT behandeling te testen. De resultaten van de eerste cases (N = 3) die behandeld zijn met BoNT worden in dit hoofdstuk besproken.
Gedurende 4 maanden werden drie kinderen met CP en ernstig kwijlen na de behandeling gevolgd. De resultaten waren gunstig. De speekselproductie vertoonde, ten opzichte van baseline, een reductie van maximaal 51 tot 63%. In alle 3 de gevallen was het effect meetbaar tijdens de eerste speekselvloedmeting 2 weken na de injecties. Het tijdstip van het maximale effect verschilde per kind en varieerde van 4 tot 16 weken. De vermindering van de speekselproductie leidde in 1 geval tot stoppen van het kwijlen gedurende de hele studie, in 1 geval nam het kwijlen aanzienlijk af en bij het laatste kind was er een lichte vermindering van het kwijlen overdag maar een forse afname gedurende de nacht. Door alle ouders werden de veranderingen als zeer positief ervaren. Bij 1 kind werd een tijdelijke indikking van het speeksel gezien, hetgeen niet tot complicaties leidde.
Op basis van deze bevindingen werd de aanbeveling gedaan om een studie te verrichten bij een grotere groep kinderen.

Hoofdstuk 7 en 8: Botuline toxine injecties bij de behandeling van kwijlen
In de hoofdstukken 7 en 8 worden de resultaten van de Botuline Toxine behandelingen in een grotere groep van 45 kinderen beschreven. Deze kinderen namen deel aan een 'controlled clinical trial'. De toepassing van een standaard behandeling (scopolamine) werd vergleken met de experimentele behandeling (Botuline Toxine injecties). Figuur 1.7 laat het verloop tijdens het onderzoek zien. Tijdens het onderzoek vielen 6 kinderen af. De gegevens van 39 kinderen werden geanalyseerd.
Tijdens de baselineperiode werd de speekselvloed en de mate van het kwijlen bij alle patiënten diverse keren gemeten. Daarop volgde de eerste behandelfase met 10 dagen Scopoderm-TTS® (Novartis Consumer Health BV, Breda, Nederland). Scopoderm is een anticholinergicum dat middels een pleister via de huid wordt toegediend en daarna via de bloedbaan verschillende organen bereikt. Na stoppen van de Scopoderm en een uitwasperiode van 4 weken werd éénmalige BoNT geïnjecteerd in de glandulae submandibularis, waarvan de dosering was gerelateerd aan het lichaamsgewicht en varieerde van 30 tot 50 U Botox®, verdeeld over de beide speekselklieren. Uitsluitend de glandulae submandibularis werden geïnjecteerd omdat deze klieren in een rustsituatie circa 60 – 70% van de speekselproductie verzorgen.

De speekselproductie van de glandula parotis en van de glandula submandibularis beiderzijds werd met regelmatige intervallen gemeten d.m.v. de wattenmethode (ml/min). Niet van alle meetmomenten waren de waarden bruikbaar, bijvoorbeeld omdat een kind verkouden was op het moment van meten. Tijdens de analyses werd speciaal aandacht besteed aan de statistische methodes om de betekenis van de missende waarden in de conclusie te verantwoorden.

Hoofdstuk 7 beschrijft de effectiviteit van BoNT op de speekselproductie bij kwijlende kinderen met een CP. Het verschil tussen de speekselproductie tijdens Scopoderm en na de Botox® injecties werd onderzocht.
Het bleek dat de speekselproductie tijdens de uitwasperiode, na de eerste behandeling met scopolamine, weer terugkeerde naar het niveau van de baselinemetingen (p = 0.733; 95% confidence interval of the difference –0.0582 to 0.0821). Dit betekent dat de duur van de uitwasperiode na scopolamine voldoende was.
Scopolamine gaf een speekselreductie van 24.7% en BoNT 42%. Ten opzichte van baseline bleek de verschilscore voor scopolamine (p = 0.001) en voor BoNT ($p \leq$ 0.002) significant. Voor BoNT werd de maximale reductie behaald bij respectievelijk 2, 4 en 8 weken ná de injecties. Ook bleek BoNT bij de metingen na 2,4 en 8 weken een significant betere speekselreductie te geven dan scopolamine ($p \leq 0.014$).
Als maat voor het succes van de behandelingen werd aangenomen dat de speekselproductie in vergelijk met baseline meer dan 30% moest afnemen. Onder deze aanname bleek scopolamine bij ~95% van de kinderen effectief te zijn. Het succespercentage 2 weken na de Botox injectie bedroeg ~70% en nam geleidelijk af tot ~49% na 24 weken.

De volgende centrale onderzoeksvraag was of het 'kwijlen' zou afnemen als de speekselproductie verminderde. Dit wordt in hoofdstuk 8 beschreven.
De mate van kwijlen werd geëvalueerd met de Drooling Quotiënt (DQ), de Teacher Drooling Scale (TDS) en aan de hand van Visueel Analoge schalen (VAS). De DQ is een observatie methode waarbij de vorming van nieuw speeksel aan de rand van de lippen of op de kin iedere 15 seconden wordt gescoord gedurende 10 minuten. Uit de positieve scores van de totaal 40 observaties werd een percentagegetal berekend, hetgeen de uitkomstmaat voor het onderzoek vormde. De TDS is een 5 puntsschaal die op basis van informatie, verkregen van ouders, de ernst van het kwijlen uitdrukt. De VAS werden gebruikt om op een aantal stellingen of vragen een waardeoordeel te verkrijgen van de ouders over het kwijlen in de thuissituatie.

Uit de analyses bleek dat de uitwasperiode na scopolamine voldeed. Er bleek geen verschil in DQ tussen de meting op baseline en die ná 'uitwassen' van scopolamine ($p = 0.32$). Deze bevinding minimaliseert het risico dat er een overdrachtseffect kon bestaan van scopolamine naar BoNT.
Het bleek dat een verminderde speekselproductie (hoofdstuk 7) grote overeenkomst vertoonde met de vermindering van het kwijlen (hoofdstuk 8). Alle metingen van de DQ na scopolamine en BoNT vertonen een significante verandering in vergelijk met de baselinemetingen ($p < 0.001$). De grootste afname van het kwijlgedrag werd 2 weken na de BoNT injecties bereikt. Echter na 24 weken, het eindpunt van de studie analyses, werd bij een deel van de populatie nog steeds een aanmerkelijk effect gevonden.
Als maat voor succes ten aanzien van het kwijlgedrag werd gedefinieerd dat er in vergelijk met baseline een reductie van 50% in de DQ moest optreden bij de metingen na behandeling met respectievelijk scopolamine en BoNT. Tijdens scopolamine kon 53% van de kinderen worden aangemerkt als responder. Twee weken na BoNT was dit percentage 64.1%. Bij 24 weken liep dit geleidelijk terug tot 48.7%. De resultaten van de TDS en de VAS kwamen overeen met de uitkomsten van de DQ.

Hoofdstuk 9: posterior drooling
'Anterior drooling' is het onwillekeurig speekselverlies uit de mond. Onder 'posterior drooling' wordt de lekkage van speeksel over de tongbasis in de hypopharynx verstaan. Posterior drooling kan tot ernstige complicaties leiden. Tengevolge van pharyngeale slikstoornissen kan chronische aspiratie het gevolg zijn. Dit veroorzaakt bij een onbekend aantal kinderen met een cerebrale parese een recidiverende pneumonie.
Tevens bestaat een bedreiging door een gastro-oesophageale reflux met o.a. indirecte aspiratie van voedsel in de bovenste luchtwegen. Het is aannemelijk dat een relatie bestaat tussen een gastro-oesophageale reflux en een toename van de speekselvloed.
Een patiënt wordt beschreven bij wie herhaalde injecties met BoNT zijn gegeven in verband met posterior drooling. Een rolstoelgebonden jongen van 9.4 jaar oud met een spastisch athetotisch beeld, werd op de polikliniek gezien i.v.m. ernstig kwijlen. Hij bleek de laatste 2 jaar gemiddeld 7 recidiverende pneumonieën door te maken. Vanwege de gepresenteerde problematiek werd deze patiënt geïndiceerd voor een dubbelzijdige injectie met Botuline toxine in de glandulae submandibularis.
De injecties resulteerden in een aanzienlijke afname van de speekselproductie en een afname in het zichtbare kwijlen, gemeten met de DQ en de TDS.
De grote winst bleek te liggen in het uitblijven van longontstekingen en dat de conditie

van de patiënt aanmerkelijk verbeterde. Op geleide van de klinische symptomen van het posterior drooling werd hij vervolgens met intervallen van 7 maanden en 12 maanden herhaald geïnjecteerd.

Hoofdstuk 10: kwaliteit van leven in relatie met kwijlen
De invloed van kwijlen bij spastische kinderen op de kwaliteit van leven werd geëvalueerd middels een uitgebreide vragenlijst die speciaal voor dit doel was ontwikkeld. De ouders van de deelnemende kinderen werd verzocht vóór en ná een behandeling met anticholinergische medicatie een vragenlijst in te vullen. Van 42 kinderen werden de gegevens ontvangen en verwerkt. In de ontwikkelingsfase van de vragenlijst zijn specifieke dagelijkse situaties geïdentificeerd die aanleiding geven tot toename van het kwijlen. Ten gevolge van de behandeling nam het kwijlgedrag in deze situaties af. De zorgbehoefte nam tevens af en de tijdsbesteding door ouders verbeterde. Het bleek minder nodig de kin en mond af te vegen en slabber of het sjaaltjes te verschonen. Er ontstond minder schade aan communicatieapparatuur en computers.
Het op deze wijze inventariseren van aspecten van de kwaliteit van leven leverde zinvolle informatie op ten aanzien van de behandelingseffecten.
In feite zouden alle therapieën, chirurgisch of niet chirurgisch, op deze wijze moeten worden geëvalueerd om zicht te krijgen en op de effecten van het kwijlen op de kwaliteit van leven van zowel kind als omgeving.

Hoofdstuk 11: algemene discussie
In hoofdstuk 11 wordt een algemene discussie gevoerd en worden aanbevelingen gegeven voor verder onderzoek.
De doelstelling van deze studie was om het effect van Botuline Toxine op de speekselproductie te vergelijken met een ander anticholinergisch medicament (scopolamine) dat al vaker als behandeling werd toegepast. Aangetoond werd dat BoNT, gespoten in de speekselklier, de speekselproductie substantieel vermindert. Het percentage kinderen met een positieve respons bedroeg op de korte termijn 70% en voor de langere termijn 50% (circa 6 maanden). Voor de patiënten die ook nog na deze tijd konden worden gemeten bleef de gunstige trend aanwezig tot 48 weken na de BoNT behandeling. Gebaseerd op anderen onderzoeken lijkt het aannemelijk dat de werking van BoNT in het autonome zenuwstelsel langer aanhoudt dan in het willekeurige zenuwstelsel.
Als niet gegeten en gedronken wordt bestaat de speekselproductie in een rustsituatie

voor circa 70% uit submandibulair speeksel, 25% uit de glandulae parotis en 5% uit de glandulae sublingualis. In dit onderzoek werd gekozen om uitsluitend de submandibulaire klieren te injecteren met BoNT. De resultaten bevestigden dat de 'rust' speekselproductie voor een groot deel door de submandibularis klieren wordt verzorgd. Als een speekselreducerende ingreep gewenst is i.v.m. kwijlen bij kinderen met een CP dan is een eerste benadering met injecties in de submandibulaire klieren een logische stap.
In de literatuur wordt in toenemende mate een pleidooi gehouden voor het injecteren van de parotiden omdat dit anatomisch gezien de grootste speekselklieren zijn en omdat ze tijdens eten en drinken in korte tijd, zeer veel sereus, waterig speeksel, kunnen produceren. Het is echter niet aan te raden om primair deze klieren te behandelen omdat dat gemiddeld ~ 1/3 van de kinderen met een CP al een gestoorde mondmotoriek heeft en derhalve moeite ondervindt met de verwerking van voedsel. Bij onvoldoende resultaat na injectie van de submandibularis kan men overwegen om de parotiden gedeeltelijk aanvullend te behandelen. De ontwikkeling van richtlijnen hiervoor is een uitdaging voor verder onderzoek.

In het verleden zijn chirurgische ingrepen veel toegepast. Deze zijn voor geselecteerde gevallen nog steeds aangewezen. In principe worden dergelijke ingrepen gedaan om definitief tot een vermindering van speekselproductie te komen, of het speeksel op een anatomisch andere plaats aan te bieden zodat het beter verwerkt kan worden. Ongepubliceerde observaties (afdeling mond- en kaakchirurgie, Catahrina ziekenhuis te Eindhoven) suggereren dat bij verwijdering van een speekselklier er compensatie van speekselproductie kan optreden vanuit de resterende speekselklieren die na enkele maanden meer zouden gaan produceren. In ons onderzoek is compensatie vanuit de parotis klieren is niet waargenomen (Figuur 7.2).

Op drie manieren werd een positieve reactie op de aangeboden behandelingen gedefinieerd.
De eerste definitie had als eis dat ten opzichte van baseline de speekselproductie met 30% moest verminderen. Er bleek een verschil te bestaan tussen het succespercentage op Scopolamine en BoNT, ten gunste van scopolamine. Bij nadere analyse van de data bleek dat een vrij groot aantal van de niet-reagerende patiënten op BoNT zeer dicht tegen de 30-procents grens aanzat.
De tweede definitie voor succes verlangde dat ten opzichte van baseline de DQ, als

maat voor het kwijlen met tenminste 50% zou verminderen. Bij deze analyse vielen de cijfers gunstiger uit voor BoNT.

De derde definitie bestond uit een samenvoeging van de eerste en de tweede definitie. Om als responder aangemerkt te worden moest ten opzichte van baseline 30% reductie in speekselproductie en 50% reductie in kwijlen behaald worden. Dit moest tenminste gescoord kunnen worden op een van de meetmomenten op BoNT-2, BoNT-4 of BoNT-8. Deze definitie aanhoudende was het algehele succes percentage 74.4% voor BoNT.

Gegeven het aantal patiënten dat aan dit onderzoek deelnam was subgroepanalyse niet mogelijk. Statistisch kon niet worden vastgesteld of anatomische factoren, mondmotorische vaardigheden, de mentale ontwikkeling, de mate van spasticiteit of omgevingsfactoren van invloed waren op het al of niet positief reageren op behandeling.

Bij langdurige denervatie van het klierparenchym (door BoNT) wordt op theoretische gronden hypotrofie van het weefsel verwacht. De klinische indruk is dat het volume van de geïnjecteerde speekselklieren afnam. Dit vormt een onderwerp voor nader onderzoek.

Tijdens de toediening van Scopolamine werden in ~82% van de gevallen bijwerkingen gezien. Het meest werd melding gemaakt van een droge mond, onrust, verwardheid en gestoorde visus. Er werden weinig en overwegend milde bijwerkingen na de BoNT injecties gezien. Twee patiënten vertoonden een griepachtig gevoel en 2 andere patiënten meldden lichte slikklachten tot enkele uren na de behandeling. Dit werd toegeschreven aan een lokale zwelling van de speekselklier. Op basis van de geobserveerde bijwerkingen kan gesteld worden dat de behandeling met BoNT weinig risico kent.

Een uitdaging voor de nabije toekomst is om de BoNT injecties bij de behandeling van ernstig chronisch kwijlen een juiste plaats te geven tussen de conservatieve en chirurgische therapieën. Verder moet onderzocht worden welke factoren de aard en de ernst van het speekselverlies bepalen om vervolgens te komen tot een therapeutische beslisboom.

Dankwoord

Veel mensen hebben bijgedragen aan dit proefschrift. In de loop van de tijd ben ik onder de indruk geraakt van de belangeloze inspanning die mensen opbrachten om het project telkens een stukje vooruit te helpen. Ieder op zijn eigen terrein. Onnodig te zeggen dat dit bewerkelijke onderzoek zonder deze inzet, niet zou zijn gelukt. Ik wil allen hiervoor hartelijk danken. Op het gevaar af mensen ongenoemd te laten wil ik me er toch aan wagen een aantal van hen met name te noemen. Om geen pijnlijke keuzes te hoeven maken, zal ik dit chronologisch doen. Anders gezegd; in "volgorde van opkomst" bij dit drooling project.

Lieve Lina, in de loop van de jaren zijn al heel wat ideeën over promotieonderwerpen de revue gepasseerd. De dreiging van een promotietraject heeft al geruime tijd boven onze relatie gehangen. In de gesprekken daarover ben je altijd stimulerend geweest en belichtte op reële wijze ook de gezinsbelangen. Het is goed gegaan en ik ben je intens dankbaar voor je steun en interesse. Menigmaal hebben we gesproken over de ins en outs van het project en ik heb ronduit kunnen profiteren van de adviezen van iemand die "een beetje van buitenaf" meekeek en meedacht, met een goede dosis mensenkennis en gevoel voor verhoudingen. In mindere tijden was je er met je persoonlijke steun. Gewoon bedanken zou te weinig zijn. Bovendien schijn ik de postpromotionele "dip" nog te krijgen. Het zal wel druk blijven. Nu het voorbij is weet je dat ik heel wat plannen heb om de tijd te gaan vullen. Daar hoort lekker samen er op uit trekken zeker bij. Altijd jouw wens, en trouwens ook de mijne, al klinkt dat misschien ongeloofwaardig omdat gezelligheid het jarenlang heeft moeten afleggen tegen dit project.

Lieve Femke, geweldig, zoals je mee bent gegroeid met dit project. Je toonde je steeds nieuwsgieriger en je vragen over het onderzoek werden steeds verfijnder. Ik ben er trots op dat ik als vader dit met jou heb mogen delen. Net als het onderzoek, ben jij in die jaren volwassen geworden en ik hoop dat onze wederzijdse intellectuele belangstelling zich zal blijven verdiepen.

Roeland: Jij bent in deze jaren uitgegroeid van beginnende puber die na een voordracht vroeg: 'Wat had je voor cijfer', tot iemand die door zijn reacties op het onderzoek te kennen geeft te beseffen wat het kan betekenen als je opgroeit met een handicap. Beiden hebben we zitten ploeteren; jij aan je examen en ik aan mijn proefschrift: Brothers in arms!

Drs. R.A.J. Rijken, beste Dick. Bij jou heb ik de opleiding tot revalidatiearts kunnen volgen. Als geen ander heb jij mij bijgebracht dat het belangrijk is dokter voor de patiënt te zijn maar daarnaast wetenschappelijk onderzoek te doen. En als het aan jou lag, om je eigen worden te gebruiken, "een stuk onderzoek waar de patiënt iets aan had". Je was dan ook erg teleurgesteld toen ik het project over de preventieve nachtelijke beademing bij de N.M.A patiëntjes niet meer haalbaar achtte. Wel nu, een beetje later in mijn carrière, ik hoop dat het met dit proefschrift is goed gemaakt. Ik dank je voor de motiverende toewijding tijdens de opleiding.

Mijn eerste promotor professor J.J.Rotteveel, beste Jan. Ik herinner mij goed dat we in de loop van 1999 serieus plannen maakte voor mijn promotie. Hoewel niet de hoogleraar van mijn afdeling (die hadden we toen niet) wilde je dat ik promoveerde met als hoger doel mijzelf en de revalidatiegeneeskunde vooruit te helpen. De behandeling van spasticiteit had ons beider belangstelling en het is specifiek jouw verdienste om het kleine maar klinisch en sociaal belangrijke onderwerp van "drooling" eruit te lichten en bij mij te introduceren. Het was wennen aan het idee dat ik over een mogelijke behandeling van kwijlen zou publiceren. Zelfs over dat wennen hebben we boeiende, soms hilarische gesprekken gevoerd. Binnen korte tijd hadden we een kundige groep om ons heen en startte het project. Goede herinneringen bewaar ik aan de befaamde avondvergaderingen die ik wellicht nog ga missen ook. Onder het genot van een glas wijn zijn op die avonden vele ideeën naar voren gekomen. Consequent en consistent heb je leiding gegeven aan het project en de goede weg bewaakt. Jan, zonder jou was het niet gelukt. De promotie is teneinde, de samenwerking en de vriendschap gelukkig niet. Samen hebben we onderwerpen genoeg voor onderzoek en met name ook de zorg rondom het kind met bewegingsstoornissen.

Mijn tweede promotor professor F.J.M. Gabreëls, beste Fons. We kennen elkaar al sinds 1986. Ik was toen assistent niet in opleiding en jij de vaste consulent van de St.Maartenskliniek. Later werd ik, inmiddels revalidatiearts, consulent binnen het 'interdisciplinair kinderneurologisch centrum'. Op jouw afdeling heb ik me altijd, mede dankzij jouw belangstelling, zeer welkom gevoeld. Het was dan ook logisch dat jij toetrad als vast lid van de droolinggroep. Ik heb genoten van je beschouwingen op onze avondvergaderingen. Bij het raamwerk voor het proefschrift zelf heb ik dankbaar gebruik gemaakt van jouw visie.

Mevr. K. van Hulst, lieve Karen. Wat hadden we zonder jou gemoeten; er zou zeer beslist geen project zijn geweest. Altijd aanwezig, opgewekt, origineel, meedenkend, kritisch, betrokken, begaan met de kinderen en hun ouders, nuchter, consequent, waarschuwend, organiserend, attent, humoristisch om maar een paar van je aangename eigenschappen te noemen. Jouw inzet is feitelijk niet met een bedankwoordje af te doen. Het was ronduit een voorrecht om met jou die 4 jaar te kunnen werken. Het is bijna niet voor te stellen hoeveel maal jij het onderzoek bij de kinderen hebt herhaald. Jij was het die de contacten onderhield met de verpleegafdelingen en het laboratorium. De ouders hebben veel aan je gehad door je vertrouwenwekkende manier van optreden en de vele nuttige adviezen die je tussendoor wist te geven. Ik stel voor dat we gewoon doorgaan met samenwerken.

Ook dank aan Mevrouw C. Godschalk, beste Carla. Als tweede logopediste was je tijdelijk betrokken bij het drooling project. Je bleek goed te zijn in het maken van schema's waardoor alles nog overzichtelijk werd. Dank voor je inzet voor de kinderen.

Drs. J. van der Burg, beste Jan. Voor dat het project startte vroeg ik of je zin had om mee te doen. Daar hoefde je niet over na te denken en gaf direct een positief antwoord. Ik dank je voor al die keren dat je met mij de discussie wilde aangaan. Je intellectuele humor heeft me menig maal op de been gehouden en gestimuleerd. Je betrokkenheid is groot geweest en het mes snijdt in dit geval wellicht aan twee kanten. In feite heb jij een parallel onderzoek opgezet waar gelukkig voor jou veel mogelijkheden inzitten. Met veel belangstelling zal ik de ontwikkelingen volgen.

Mevr. R. van der Heijden, beste Ricky. We kennen elkaar al zeer lang en je bepaalde in de begin jaren '90 in feite het gezicht van de revalidatie in het "Radboud". Je aankondiging om te stoppen met werken zat me niet lekker en op slinkse wijze heb ik je tot over je oren in het drooling project kunnen trekken. Daar heb je nog mooi ruim 3 jaar aan vastgezeten. De organisatie lag bij jou en met het 'IKEA'-meetlint heb je heel wat afspraken uitgezet op de jaarkalender. Dank voor de oplettende houding en de goede organisatie. Jouw inzet ging ver. Zelfs 's avonds werd je door de ouders gebeld op de 06-nummer (dat ik hier niet zal herhalen). Thuis hadden ze mogelijk wel genoeg van de drooling-telefoon. Samen met Karen heb je er op fantastische wijze voor gezorgd dat het allemaal mogelijk werd. We zijn dikke vrienden geworden en ik zal je nooit vergeten.

Mijn volgende woord van dank gaat uit naar de ouders die zoveel vertrouwen hebben gesteld in ons drooling project en er ontzettend veel voor over hadden om uit alle windstreken voor behandeling en controles te komen. De kinderen die telkens weer bloot werden gesteld aan nare onderzoeken met van die watten in hun mond. Wat fantastisch dat jullie dat allemaal gedaan hebben. We weten nu dat het merendeel van jullie goed op de behandeling kan reageren. Voor enkelen was het resultaat minder, maar daar werken we nog aan!!!!

Mij eerste co-promotor dr. J. van Limbeek, beste Jacques. Je hebt als geen ander invulling gegeven aan de statistische analyses voor het project. Je gaf ruiterlijk toe dat je daarin af en toe wel wat eigenwijs was. En niet onterecht, zo bleek, want zonder één aanpassing en met wat toelichting hebben we samen 4 reviewers (statistici) bij Neurology weten te overtuigen. Ik heb veel van je geleerd over de benadering van een probleem, de methodologie, de statistiek en het schrijven van een goed artikel. Je fabelachtige overzicht aangaande de statistiek en methodologie gold in mindere mate voor het nakijken van een compleet manuscript; het was telkens weer genieten als je vertwijfeld over de stapels papier op je bureau keek en ik je hoorde zeggen: “waar heb ik het nou toch gelaten”. We hebben veel plezier gehad en ik snap nog steeds niet waar je, ook in de avonduren, de tijd vandaan haalde om mij bij te staan.

Mijn tweede co-promotor dr. F.J.A. van den Hoogen, beste Frank. Het heeft wel iets om je overbuurman te vragen als co-promotor. Een van je eerste grappen was ‘of de jonge promovendus wellicht in de vrije uren ook tijd had om de tuin te komen doen’. Hoewel het op sommige momenten moeilijk bleek om privé en project te scheiden is het zóver nooit gekomen. Bedankt voor je betrokken inzet en de uitmuntende correcties die je hebt gegeven op de conceptartikelen. Je hebt ervaring opgedaan in Engeland en daarom mocht jij als enige zeggen: ”Peter, ik weet wat je bedoelt, maar het staat er niet”. We bespraken het reeds, en ik zie er naar uit, om samen met Jan Rotteveel verder te gaan in dit onderwerp, ook op chirurgisch gebied. Jouw kennis en inzicht is daarbij zeer gewenst.

Dr. F. Joosten, beste Frank. In de eerste uren van het project was je erbij, tot zeer veel genoegen van alle projectleden. Prachtige plaatjes toverde je tevoorschijn op de monitor. Het ECHO-geleid prikken van Botuline Toxine in de speekselklieren bleek een voorwaarde. Met jou legde ik de basis voor de “technical note” die inmiddels in de

literatuur al vaak is aangehaald. Het was buitengewoon prettig om met je samen te werken. Bij je vertrek heb je gelukkig gezorgd voor een fijne opvolger zodat het project vlekkeloos door kon. Ik dank je voor dit alles.

Drs. L. van Die, beste Lia. Al weer heel wat keren stonden we gezamenlijk op de operatiekamers bij de KNO. We vormen een goed team en ik ga ervan uit dat we dit in de nabije toekomst kunnen voortzetten, gezien de belangstelling die er landelijk is voor onze kleine ingreep. Je hebt al eens genoemd dat je mij wilt opleiden in de ECHOgrafie zodat ik het zelf kan gaan doen. Het lijkt me een goed idee als we dat nog even uitstellen.

Drs. D. van der Schaaf, beste Dick. Het verzamelen van data is één ding, het verwerken komt daarna. Wat fantastisch dat jij computeren als je hobby hebt. We hebben genoten van je software en de vele bruikbare oplossingen en ik zal maar zeggen:"je bent nog niet van de droolinggroep af".

Mevr. P.G. Anderson, MA, beste Patsy. "NO MERCY" bleek zo'n beetje het motto te zijn waarmee je de concepten van mijn artikelen hebt bekeken en met je beruchte rode pen bewerkt. Van je opbouwende kritiek, ook op methodologisch gebied, heb ik veel geleerd.

Mevr C. Steinmann, lieve Corry. Als ik het over mijn secretaresse heb dan ben jij dat. In directe zin heb je niet zoveel gedaan voor het project omdat het hoofdzakelijk op het Radboud plaatsvond. Je werk op de achtergrond was echter fantastisch en onmisbaar. Onze samenwerking is een soort vanzelfsprekend geworden na al die jaren. Ik hoop het nog lang te kunnen voortzetten.

Frans v.d. Brandt en medewerkers van het laboratoruim. Onnoemelijk veel buisjes met speeksel hebben jullie verwerkt: klasse werk. De analyse ervan gebeurt in Amsterdam en zal onderdeel zijn van het vervolgproject.

Dr. D. Burger, apotheker, beste David. Saskia vd Velde en Anita Huisman van de apotheek. Veel energie hebben jullie gestoken in het protocol om de route van de Botuline Toxine goed te laten verlopen. Jullie waarschuwingen "de Botox is bijna op" kwamen altijd goed op tijd. Heel veel dank.

Afdeling BOB, beste Gidi, Gerard en Mea en verpleegkundigen. Met de klinische opnames en de dagbehandelingen voor de kinderen van het project hebben jullie mij een enorme dienst bewezen. Een goed geoliede afdeling met een hoog service niveau.

Medewerkers van de poli kindergeneeskunde. Jullie hebben onderdak verleend voor het doen van de metingen door Karen. Ook toen ik kamers nodig had om de kinderen voor dagbehandeling op te vangen waren jullie bereid. Dat was een goede zaak.

Voor de collegae anesthesisten op de KNO was het fenomeen kwijlen nieuw. Hartelijk dank dat jullie met zoveel flexibiliteit de 'drooling kinderen' hebben opgevangen.

Dag-unit KNO, beste Annelies, Angelique, Tineke. Wat was het telkens gezellig om even te komen buurten en lekker lang doen over het maken van de afspraken. Goeie koffie hebben jullie daar, nooit een Bosscher Bol gezien. Maar behalve de lol ook serieus gewerkt. Het was geweldig om te zien wat voor een fijne band jullie met de kinderen en hun ouders wisten op te bouwen. Het maakte het voor hen makkelijker om nog eens op herhaling te komen. De soepele organisatie en de attente houding heb ik bijzonder gewaardeerd.

Dr. C. Ingels, beste Coen. Zonder het waarschijnlijk zelf te weten heb je samen met Frank van den Hoogen veel betekend voor het drooling project, door mij in het begin ruimhartig tijd op jullie dag-unit en OK te gunnen.

Verpleegkundig operatie Team KNO/kaakchirurgie, beste Ireen, Annemiek en anderen. Het was eng toen ik de eerste keer met het gevaarlijk Toxine op de OK kwam, maar de noodzakelijke voorzorgsmaatregelen waren snel in het programma opgenomen. Uit de reacties merkte ik tot mijn vreugde dat het drooling project na enige tijd echt ging leven op de OK. Bedankt voor de ondersteuning in de zoektocht naar mogelijkheden om de kinderen telkens weer in het programma te krijgen.
Ook dank aan Mieke Peters voor het telefonisch overleg en de accurate planning.

Collegae en secretaresses van het Radboud. Beste Henk & Henk, Annet en Mirjam. Jullie stimulerende woorden waren af en toe hard nodig, het deed me goed. Bedankt voor de waarnemingen. Ik kan het niet vergoeden, helaas. Henk van de Meent, ik

verwacht dat je interesse in kinderen met bewegingsstoornissen in de toekomst zal leiden tot mooie gezamenlijke projecten.
Veel dank Karin, Desiree en Francien voor het aannemen van onnoemelijk veel telefoontjes en het opmaken van moeilijke tabellen voor lezingen en manuscripten.

Drs. L. Rotteveel, beste Lisselotte. Geheel zelfstandig heb je een onderdeel van het project afgerond met de statistische verwerking van de data als hoogtepunt. Je was een kei en het artikel werd geplaatst. Reuze bedankt.

Collegae kinderrevalidatieartsen, beste Margriet en Nique. De maten op de St.Maartenskliniek. Jullie bedankt voor de support en voor de vele waarnemingen die nodig waren om mij dit onderzoek te kunnen laten uitvoeren.

De leden van de manuscriptcommissie professor G. Padberg, professor K. Graamans en professor K. Postema wil ik hartelijk danken voor het kritisch en gedetailleerd lezen van het manuscript. Het was fijn om uw positieve reacties terug te krijgen.

Ook buiten de het Universiteitsziekenhuis St.Radboud en St.Maartenskliniek hebben zich mensen ingezet en zijn steunend geweest met hun belangstelling. Te beginnen bij mijn familie, Piety voor je omslagontwerp, Rob, Johan, Emilia bedankt voor jullie steun. Speciale dank aan mijn moeder, dat je mij met belangstelling hebt gevolgd. Samen weten we het: Pa zou tevreden zijn geweest.
Bijzonder veel dank aan Tom van den Brink en Ben van der Klift: van mijn vrienden ken ik jullie het langst. Je hebt mij de eer gegund als paranimph te willen optreden. Ik bewaar goede herinneringen aan de voorbesprekingen tijdens het zeilen. Gerard de Jong, je hebt deze lange jaren niet nagelaten je bij een goed glas wijn van haver tot gort over dit onderzoek te laten informeren.
Dank voor de prettige samenwerking met professor van Nieuw Amerongen en Enno Veerman, Acta te Amsterdam.
Katleen Broeckhoven, Jannie van den Broek en Rob van den Sigtenhorst, Allergan, bedankt voor jullie onvoorwaardelijke steun.
Dierbare vrienden, iedereen die onbedoeld niet genoemd is: Hartelijk dank.

Curriculum vitae

Peter Jongerius werd op 17 November 1955 geboren in Oosterbeek en is daar opgegroeid. Binnen de mogelijkheden van de mammoetwet heeft hij alle schooltypen gevolgd op het Redichem college te Oosterbeek en later op het christelijk lyceum te Arnhem waar hij in 1976 het VWO diploma behaalde. In hetzelfde jaar begon hij met de studie geneeskunde aan de Rijks Universeit te Utrecht. In 1983 werd het artsexamen gehaald. Aansluitend was hij gedurende 2 jaar 'AGNIO' algemene heelkunde in het Overvecht ziekenhuis te Utrecht (1984/1985) en het Havenziekenhuis te Rotterdam (1985/1986). Na eerst een periode als AGNIO werkzaam geweest te zijn in het revalidatiecentrum van de Sint Maartenskliniek te Nijmegen, kon hij vanaf 1 maart 1987 aldaar de opleiding tot revalidatiearts volgen (opleider: R.A.J. Rijken) met deelopleidingen in Canisius Wilhelmina ziekenhuis en het Universitair Medisch Centrum Sint Radboud te Nijmegen. Tijdens deze periode ontstond de speciale belangstelling voor de kinderrevalidatie. Op 15 maart 1991 werd de opleiding afgerond en bestond de unieke kans om zijn eerdere medeopleider in de kinderrevalidatie, drs. R.S. Blankesteijn, op te volgen. Vanuit het revalidatiecentrum werd hij als kinderrevalidatiearts o.a. gedetacheerd naar de revalidatieafdeling van het "Radboud". Als hoofd van die afdeling (1993/2001) heeft hij met zeer veel genoegen, samen met de collegae, gewerkt aan de uitbouw van deze afdeling om de voorwaarden voor de medisch specialistenopleiding en de komst van een hoogleraar vorm te geven. Thans is hij grotendeels werkzaam in de St. Maartenskliniek met een deelaanstelling in het UMC Sint Radboud, met als speciaal aandachtsgebied de behandeling en begeleiding van kinderen met een cerebrale parese, in het kader waarvan dit proefschrift is geschreven.

In Utrecht leerde hij Lina Tacoma kennen, waarmee het liefde op het eerste gezicht was. In 1984 trouwden zij en hebben inmiddels een gelukkig gezin samen met Femke en Roeland.